RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

UIC-P - Espaces Congrès
16, rue Jean Rey - 75015 Paris

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Sous l'égide de :

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RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

Cellules Souches Thérapeutiques dans l'Inflammation

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CHU de Montpellier

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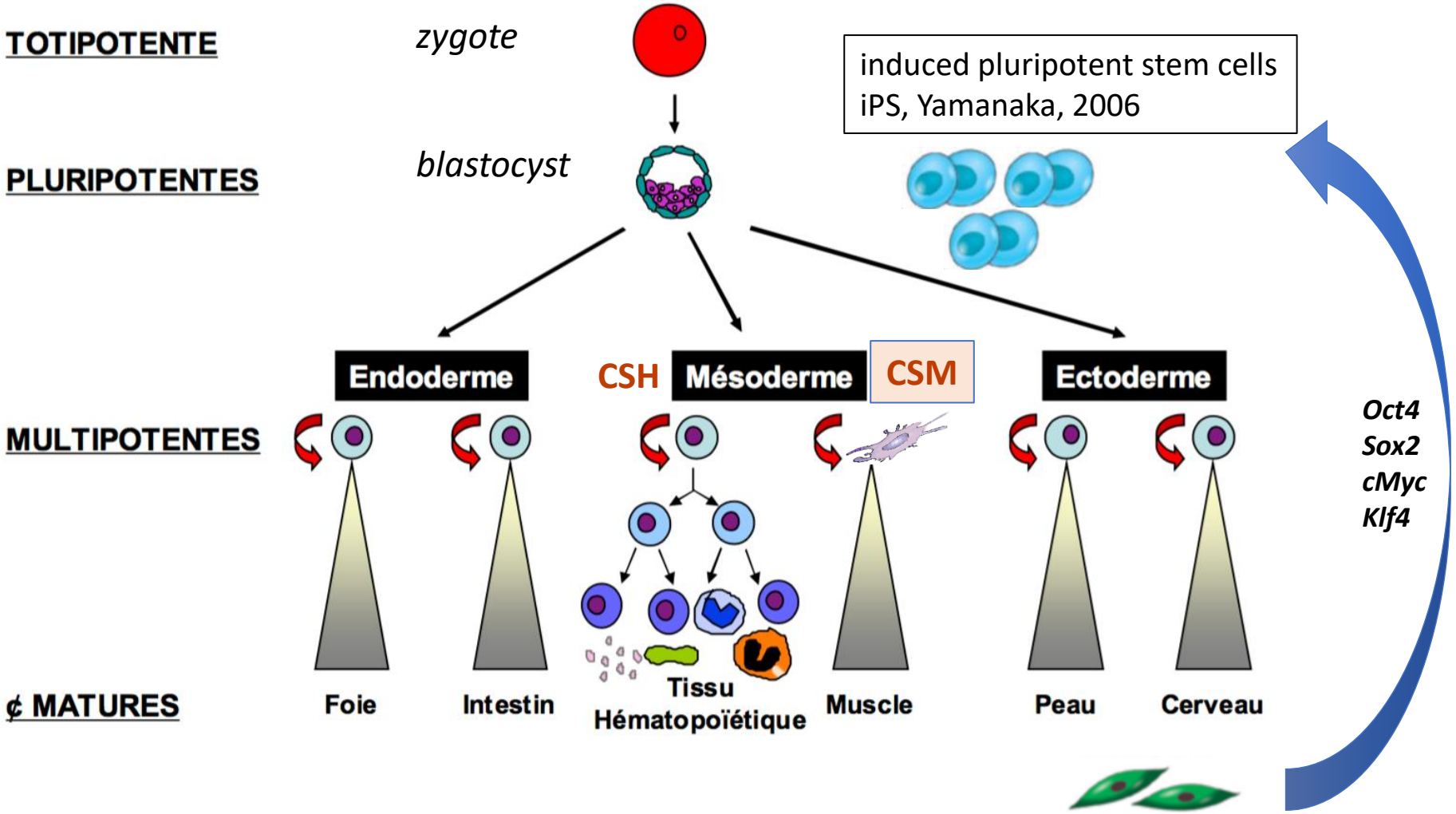
Sous l'égide de :

Aucun lien d’intérêt

Cellules souches thérapeutiques:
Cellules Stromales Mésenchymateuses Multipotentes

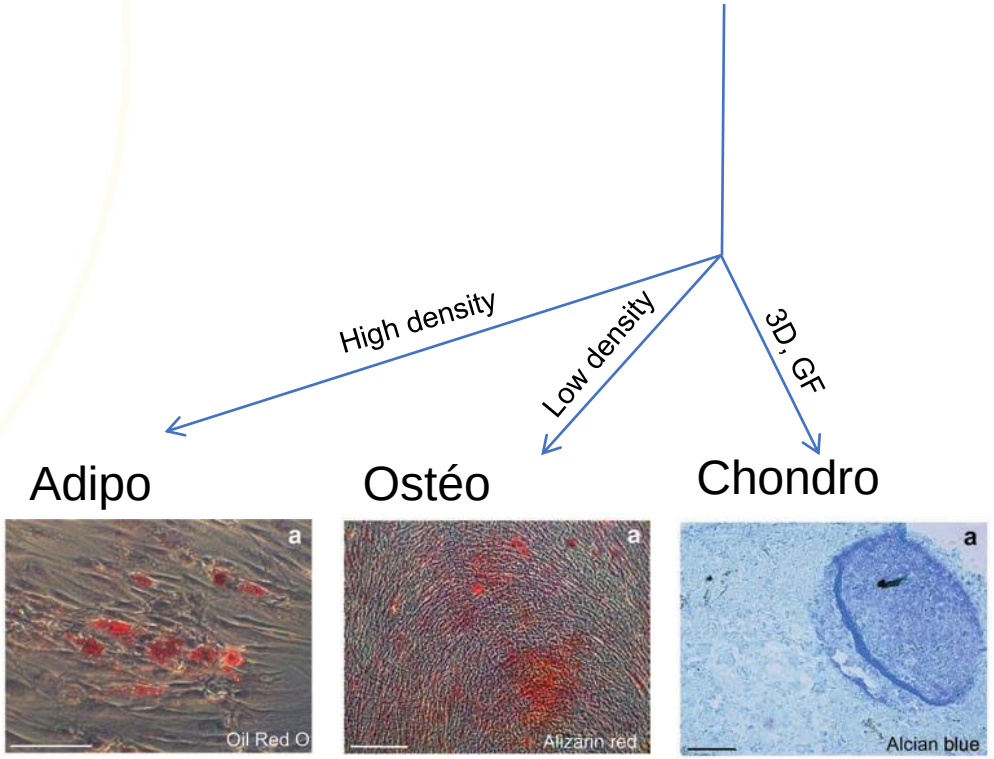


Cellules Stromales Mésenchymateuses (CSM): définition

1. **Adhésion au plastique**
   - A. Friedenstein: bone marrow (BM-MSC)
   - CFU-F : fibroblastic

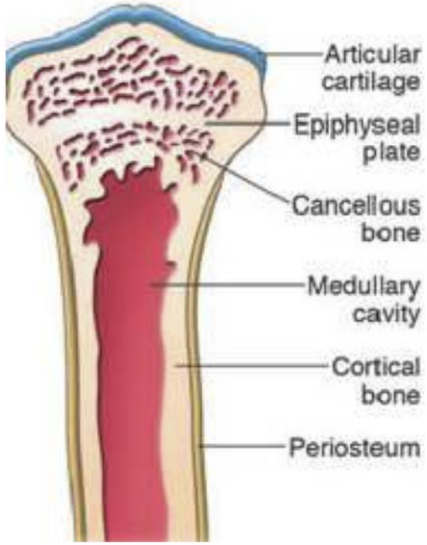
2. **Marqueurs de surface**:
   - Positivité >95%: CD73 / CD90 / CD105
   - Négativité <2%: CD45 / *CD34* / CD14 ou 11b / CD19 ou 79 / *HLA-DR*

3. **Différentiation 3 lignées:**
   - Adipocytes
   - Ostéoblastes
   - Chondrocytes

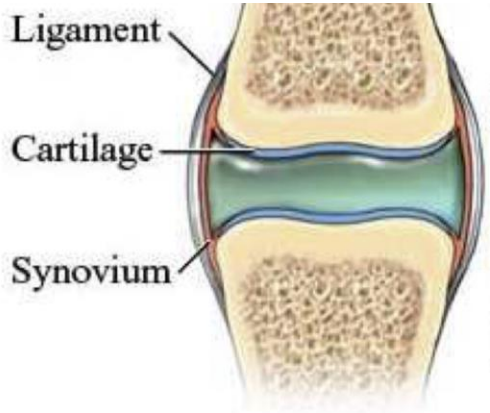


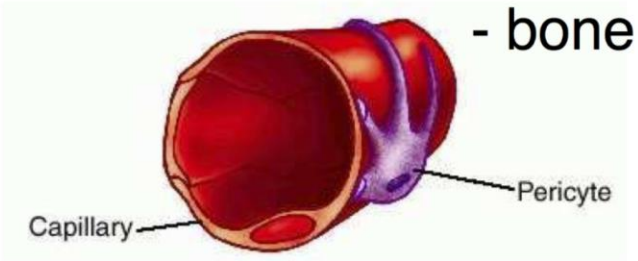
ISCT 2006

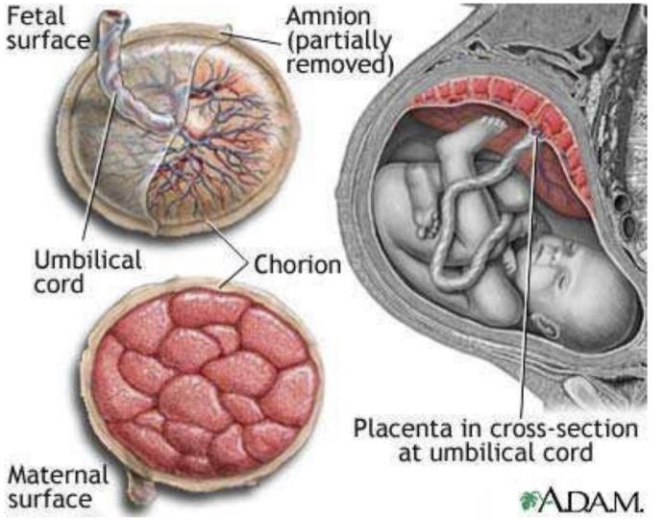
CSM: sources, origines tissulaires



- periosteum,
- perichondrium,
- synovium,
- muscle,
- lung,
- dental pulp,
- placenta,
- cord blood,
- pericytes,
- cartilage,
- adipose tissue,
- bone marrow





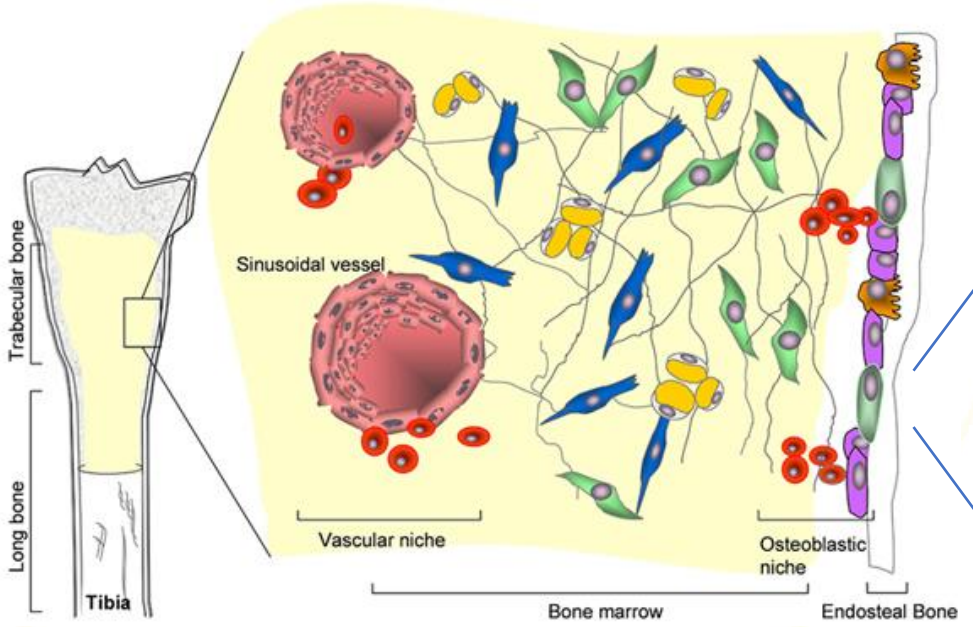


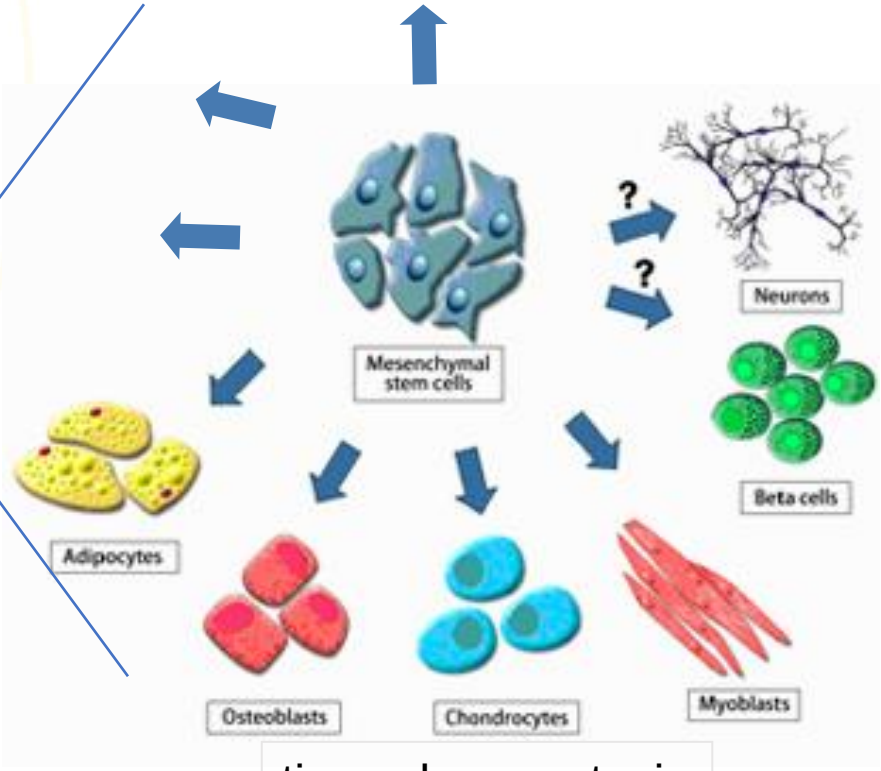
CSM: Rôles Physiologiques: homéostasie tissulaire

prevent fibrosis

prevent apoptosis

Immune cells homeostasis

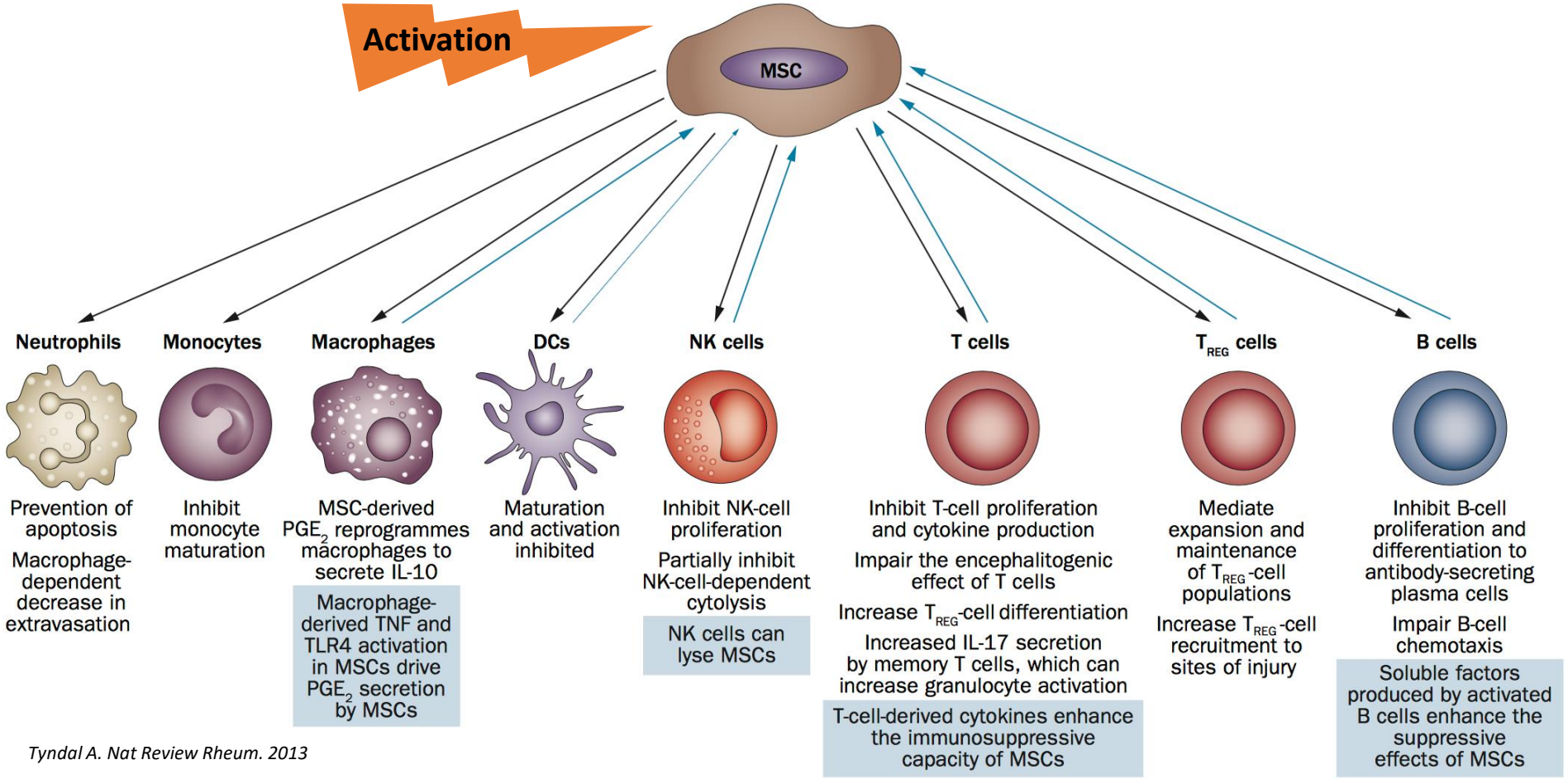




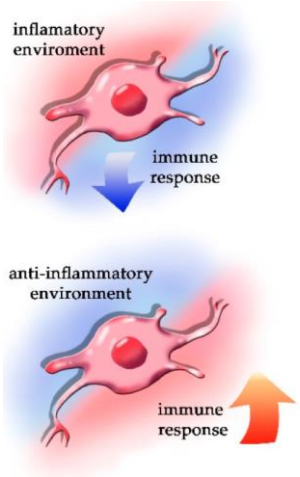
Bone marrow hematopoietic niche

tissue homeostasis

CSM: Homéostasie Immunitaire



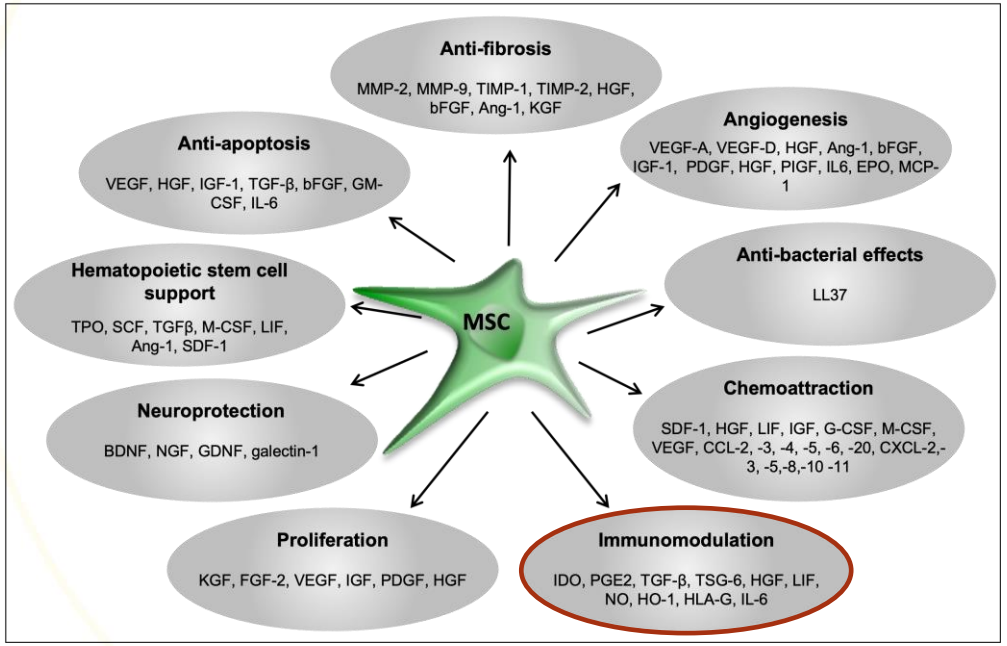
Tyndal A. Nat Review Rheum. 2013



Les CSM, « chef d'orchestre » de la réponse immunitaire

Daniela Gois Beghini et al. Cells 2021

CSM: Mécanismes d'Action et Propriétés Thérapeutiques



Paracrinie +++ >> Contacts inter-cellulaires

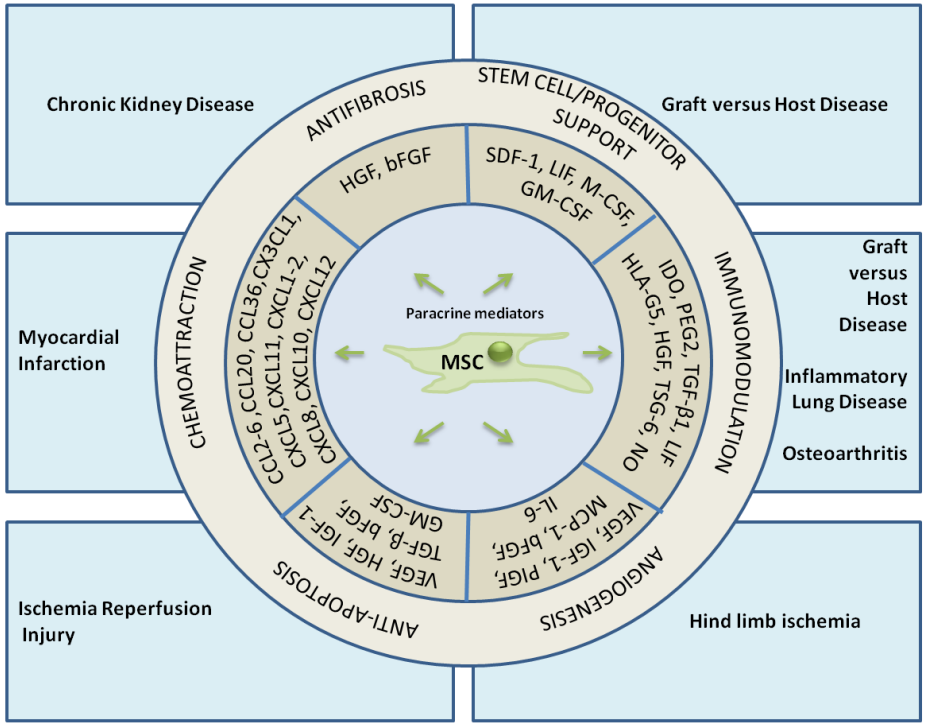


Figure 2. MSC paracrine-mediated mechanisms of action and their therapeutic relevance

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

→ **Peu/Pas d'expression des molécules HLA: « immune priviledged »**
→ **Pas de conditionnement**

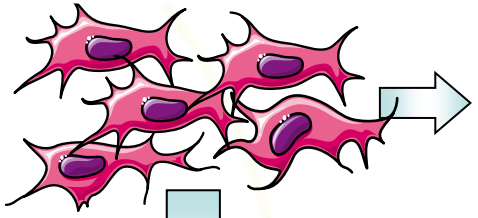
CSM: Propriétés et Applications Thérapeutiques Potentielles

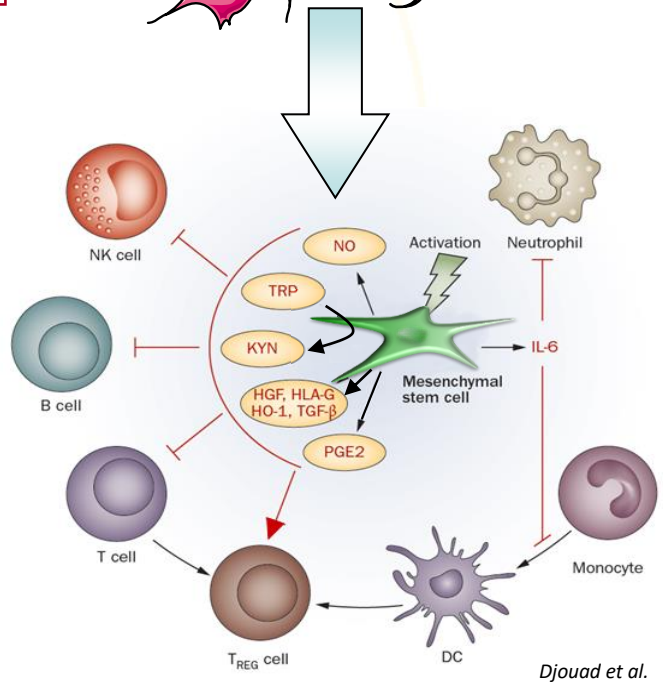
Trophicité tissulaire

1. **Anti-fibrotique**
2. **Anti-apoptotique**
3. **Angiogénique**

Stroke
Ischemic cardiopathy
Limb ischemia

Skin healing
Scleroderma





Immunomodulation

Régénération tissulaire

Ostéoblaste
Chondrocyte
Adipocyte

Bone cartilage
OA
Bone repair

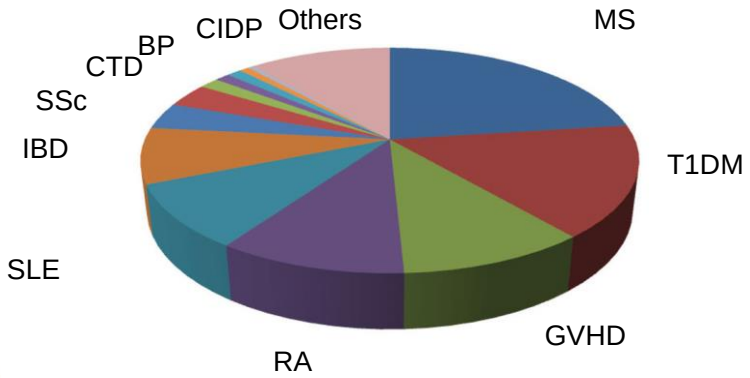
GVHD

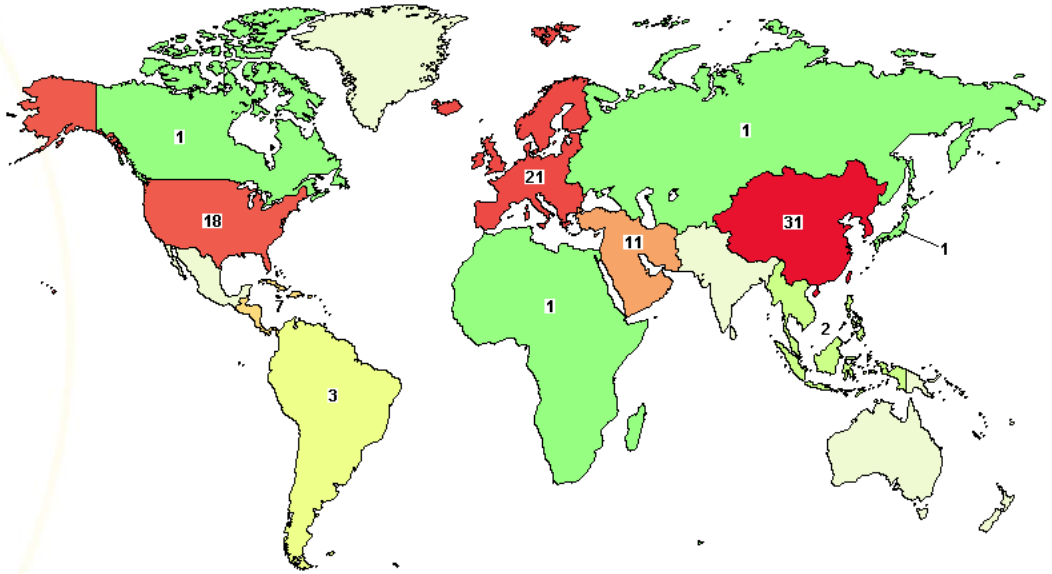
Lupus
MS
IBD
Arthritis

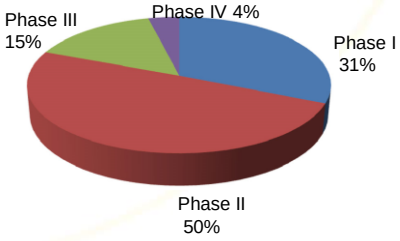
Immune Mediated Inflammatory diseases (IMID)

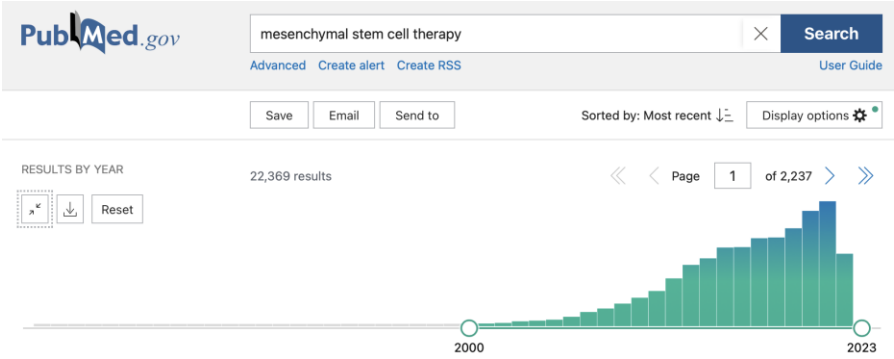
CSM: Essais Cliniques (clinicaltrials.gov)

MSC : >1400 studies (590 en 2016)
MSC + IMID: >100 studies



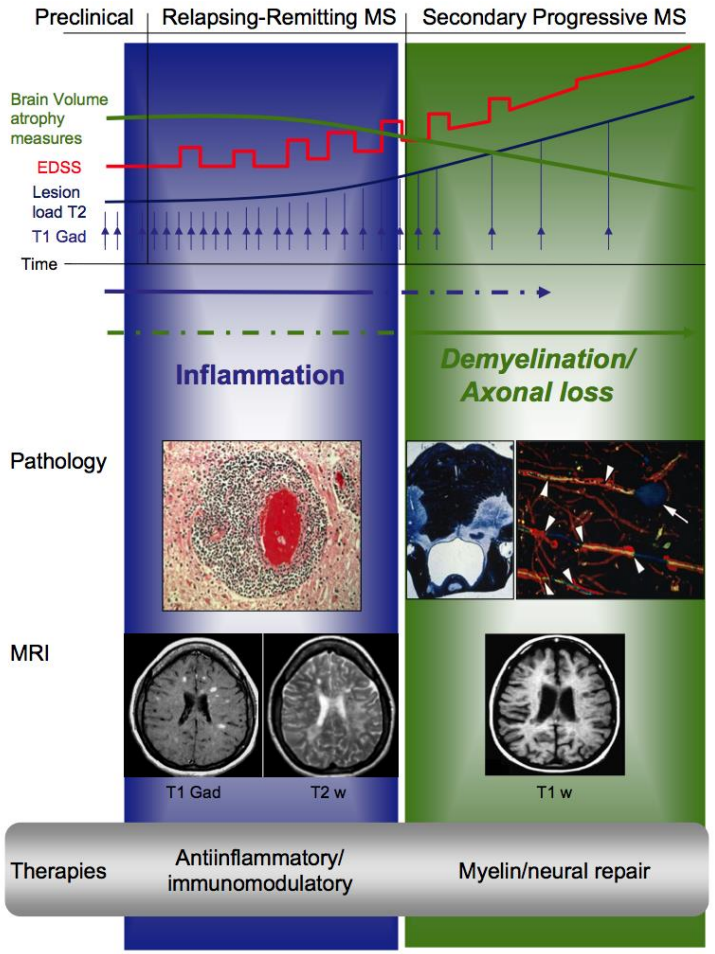






Burns
Covid-19

CSM: SEP : formes progressives +/- actives



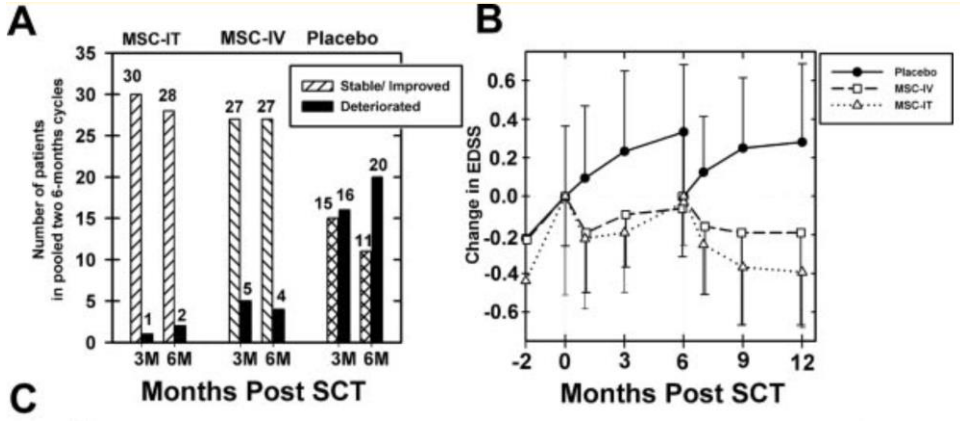
	All patients (n = 48)	MSC-IT (n = 16)	MSC-IV (n = 16)	Sham treatment (n = 16)	P-value (Kruskal-Wallis test)
Gender	28M, 20F	10M, 6F	6M, 10F	12M, 4F	0.312
Age at inclusion, years	47.63 ± 9.72	49.05 ± 7.2	47.42 ± 10.4	45.89 ± 10.9	0.566
Disease course[a]	20 active[a]: 18 SPMS, 2 PPMS	6 active[a]: 5 SPM, 1 PPMS	7 active[a]: 7 SPMS	7 active[a]: 6 SPMS, 1 PPMS	0.552
	28 non-active: 23 SPMS, 5 PPMS	10 non-active: 8 SPMS, 2 PPMS	9 non-active: 8 SPMS, 1 PPMS	9 non-active: 7 SPMS, 2 PPMS	
Disease onset (y)	12.70 ± 7.51	10.28 ± 4.48	12.90 ± 8.74	14.94 ± 8.27	0.361
EDSS increase at last year	0.73 ± 0.51	0.72 ± 0.51	0.78 ± 0.75	0.69 ± 0.57	0.641
EDSS at inclusion					0.819
Mean ± SD	5.60 ± 0.88	5.75 ± 0.77	5.63 ± 0.83	5.44 ± 1.05	
Median (IQR)	5.75 (5.5–6.5)	5.75 (5.5–6.5)	5.75 (5.5–6.5)	5.75 (4.87–6.12)	
EDSS at baseline					0.583
Mean ± SD	5.88 ± 0.80	6.19 ± 0.31	5.81 ± 0.77	5.66 ± 1.08	
Median (IQR)	6.0 (5.87–6.5)	6.0 (6.0–6.5)	6.0 (6.0–6.5)	(4.87–6.5)	
Number of previous DMT	2.58 ± 1.18	2.62 ± 1.02	2.87 ± 1.36	2.25 ± 1.24	0.403

BRAIN
A JOURNAL OF NEUROLOGY

CLINICAL TRIAL

Beneficial effects of autologous mesenchymal stem cell transplantation in active progressive multiple sclerosis

Panayiota Petrou,[1] Ibrahim Kassis,[1] Netta Levin,[2] Friedemann Paul,[3,4,5] Yael Backner,[2] Tal Benoliel,[2] Frederike Cosima Oertel,[3,4] Michael Scheel,[3,4,6] Michelle Hallimi,[1] Nour Yaghmour,[1] Tamir Ben Hur,[2] Ariel Ginzberg,[1] Yarden Levy,[1] Oded Abramsky[2] and Dimitrios Karussis[1]



1 poussée dans année et IRM+
Retraitement à 6 mois

CSM: SEP : nombreuses études

JSRM

Contents lists available at ScienceDirect

Regenerative Therapy

journal homepage: http://www.elsevier.com/locate/reth

Review

Mesenchymal stem cell therapy: A review of clinical trials for multiple sclerosis

Table 2
BM-MSCs clinical trials for MS disease.

Cell Type	Years	Country	Phase	Evaluation after Cell Therapy
Autologous BM-MSCs	2014–2016	Israel	2	Changes in immunological response at 12 months following treatment. Neurological function test and Expanded Disability Status Scale (EDSS) improvement (NCT02166021)
Autologous BM-MSCs	2015–2018	France	1 & 2	Primary outcome is safety cell therapy without side effects. Efficacy assessed by combined unique magnetic resonance imaging (MRI) activity, volume of GEL, and volume of BH (black holes) (NCT02403947)
Autologous BM-MSCs	2006–2011	UK [8,7]	1 & 2	Safety and feasibility of the intervention and informing design of future studies to address efficacy, mesenchymal stem cells in multiple sclerosis (MSCIMS) adopts a novel strategy for testing neuroprotective agents in MS – the sentinel lesion approach serving as proof of principle for its future wider applicability (NCT00395200)
Autologous BM-MSCs	2013–2017	Jordan	1 & 2	Patient with any relevant side effects observed, assessing the safety of autologous MSCs injection (NCT00781872)
Autologous BM-MSCs	2006–2009	Israel [26]	1 & 2	Safety and migration ability of the injected cells, clinical efficacy. N side effects. Transplantation of MSCs in patients with MS and ALS is a clinically feasible and relatively safe procedure and induces immediate immunomodulatory effects (NCT00781872)
Autologous BM-MSCs	2013–2016	Spain	1 & 2	Safety and efficacy after cell therapy, subsequent flow cytometry: IL-2, 4, 6, IFN-γ, IL-10, TNF-α, or by ELISA: TGF-β and IL-17 (NCT02035514)
Autologous BM-MSCs	2017	Jordan	1	Effectiveness assessment by MRI, safety assessment by physical examination, vital signs, analytical results, electrocardiograph monitoring, and EDSS (NCT03069170)
Autologous BM-MSCs	2001–2005	USA [2]	1	Four new or enhancing lesions were seen on MRI, all within 13 months of treatment. In this population with high baseline EDSS, a significant proportion of patients with advanced MS remained stable for as long as 7 years after transplant (NCT00014755)
Autologous BM-MSCs	2015–2018	Spain	1 & 2	MS therapy is safe without side effects after cell injection. Evaluated EDSS score (NCT02495766)
Autologous BM-MSCs	2013–2018	UK [52]	1 & 2	MS therapy is safe without side effects after cell injection. Evaluated EDSS score (NCT02495766)
Autologous BM-MSCs	2014–2018	UK [52,52]	1 & 2	MS therapy is safe without side effects after cell injection. Evaluated EDSS score (NCT02495766)

Table 3
AD-MSCs therapy clinical trials for MS disease.

Cell Type	Years	Country	Phase	Evaluation after Cell Therapy
Autologous ADMSCs	2018	Spain [11]	1 & 2	Infusion of autologous AD-MSCs is safe and feasible in patients with SPMS (NCT01056471)
Autologous ADMSCs	2012–2015	Sweden [6]	1 & 2	Safety of intravenous (IV) therapy with autologous MSCs in MS patients (NCT01730547)
Autologous AMDSCs	2014–2018	USA	2	Change from baseline in sexual satisfaction at month 12 as measured by participants using the SSS (Sexual Satisfaction Scale) (NCT02157064)

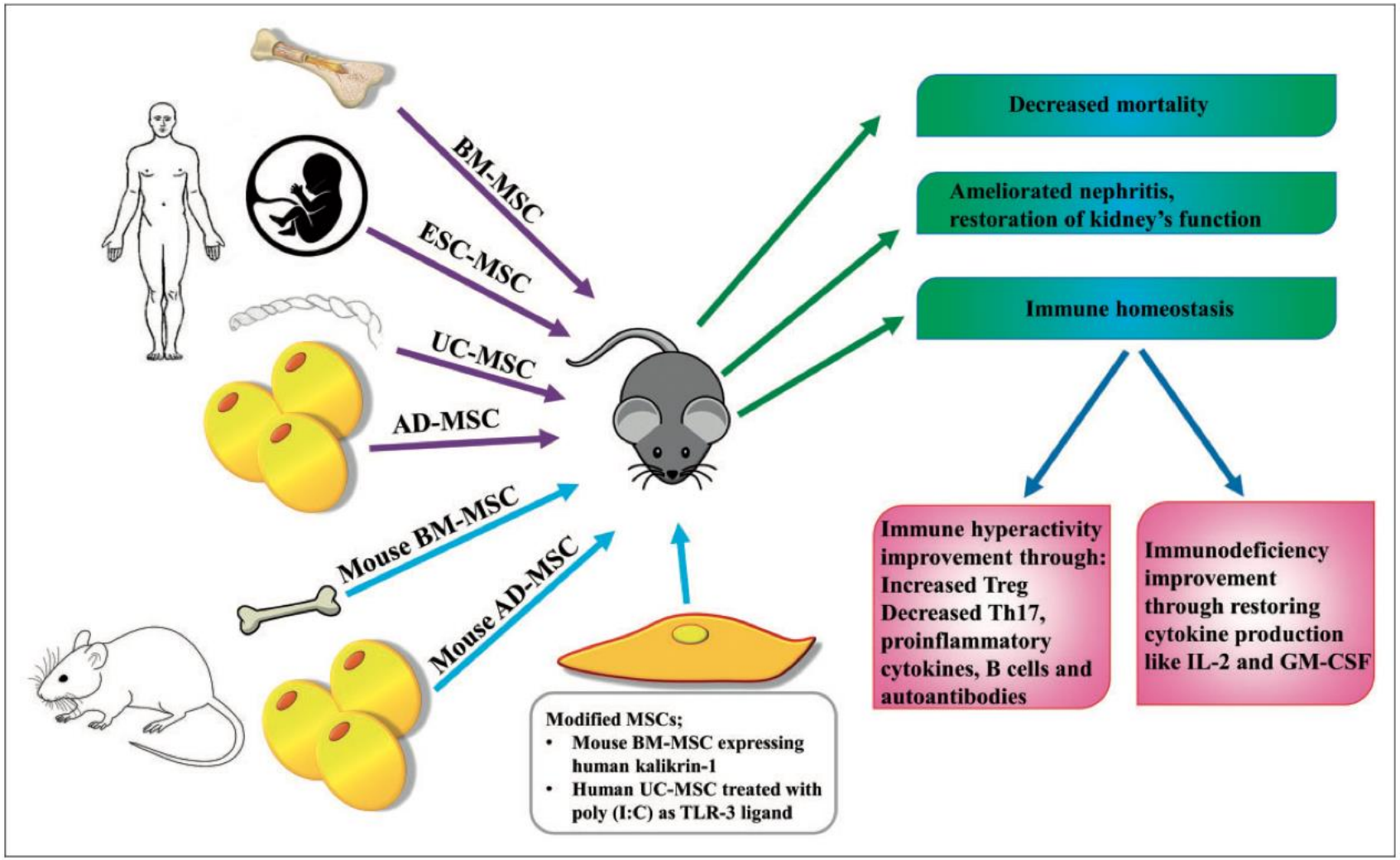
Table 4
UCMSCs therapy for MS disease.

Cell Type	Years	Country	Phase	Evaluation after Cell Therapy
Allogenic UCMSCs	2014–2017	China	1 & 2	No clinical attacks occurred during transplantation. MRI revealed a reduced number of foci and EDSS scores were decreased
Allogenic UCMSCs	2017	Jordan	1 & 2	Intensity and volume of CNS lesions assessed to investigate the therapeutic benefits of the injected allogenic MSCs and physical therapy by MRI (NCT03326505)
Allogenic UCMSCs	2014–2017	Panama	1 & 2	Change in disability as measured by EDSS, qualify of life as measured by the SF-36 quality of life questionnaire (NCT02034188)
Allogenic UCMSCs	2010–2014	China [42]	1 & 2	Evaluated core of EDSS, VEP (visual evoked potential), MRI, SEP (somatosensory evoked potential) and BAEP (brainstem auditory evoked potential). No side effects were apparent after cell injection (NCT01364246)
Allogenic UCMSCs	2018	Panama	Not specified	Gadolinium-enhanced MRI scans of the brain and cervical spinal cord were taken at baseline and also 1 year post-treatment. Treatment with UCMSCs intravenous infusions for subjects with MS is safe (NCT0234188) [54]

- ✓ Faisabilité
- ✓ Immunomodulation
- ✓ IRM
- ✓ EDSS

mais seulement phases 1/2 !!

CSM: LES : études précliniques



Fathollahi et al. Lupus 2018

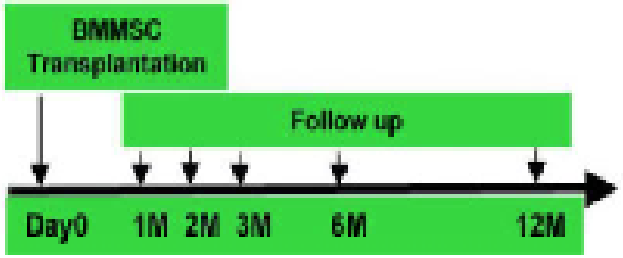
CSM: Lupus Systémique: études cliniques

- Report of 4 patients
- Refractory SLE (BILAG >8), nephritis
- allogeneic BM-MSCs (10^6/kg) from family members

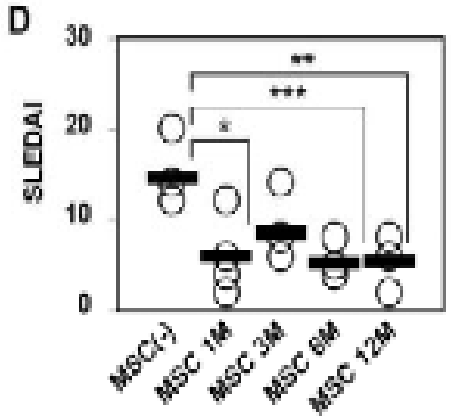
↘ Proteinuria and SLEDAI M12

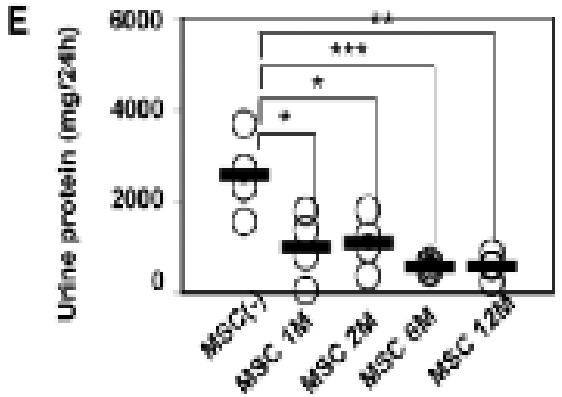
↗ **Treg CD4+FoxP3+**

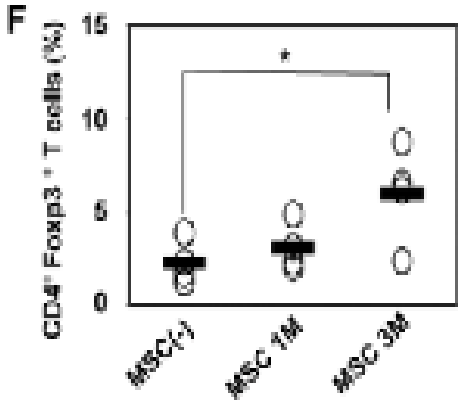
- *Confirmation sur >100 patients, 4 ans de recul, multicentrique, hématologique, hémorragie alvéolaire…*



BMMSC transplantation in SLE patients







Lingyun Sun, Stem cells 2009

Wang et al., cell transplant 2012
Wang et al., ART 2014

CSM: Lupus Systémique: résumé études cliniques

Author, year	Study type	Basic regimen	Patient characteristics	MSC	MSC dose	Infusion	Endpoint	Adverse events	Effectiveness
Yang, 2014	RCT	GC+CTX	Refractory SLE	UC-MSC	3×10^7, once	IV	SLEDAI, proteinuria, Scr, serum albumin, C3, C4	—	Yes
Zeng, 2016	RCT	GC+MMF	II-IV type of LN	UC-MSC	1×10^6/kg, 3-5 times	Renal artery	SLEDAI, proteinuria, Scr, serum albumin, C3, C4, BUN	—	Yes
Tang, 2016	RCT	GC+MMF +CTX	IV type of LN	UC-MSC	5×10^7, twice	IV	SLEDAI, proteinuria	T ($n = 2$): 1 case with upper respiratory tract infection, 1 case of right thigh abscess; C ($n = 1$): 1 case with upper respiratory tract infection	No
Deng, 2017	RCT	GC+CTX	IV type of LN	UC-MSC	2×10^8	IV	Proteinuria, Scr	T ($n = 2$): one with leucopenia and pneumonia together with subcutaneous abscess. Another with severe pneumonia; C ($n = 2$): one patient with stroke and another with ascites of unknown cause	No
Gu, 2014	Self-control	GC+CTX/MMF	Refractory SLE	BM-MSC, UC-MSC	1×10^6/kg, once	IV	SLEDAI, proteinuria, Scr, BUN	Enteritis, diarrhea, transient increase of serum creatinine, herpes virus infection. But, none of them were considered to be related to MSC infusion	Yes
Zhu, 2016	Self-control	GC+CTX/MMF	Refractory SLE	UC-MSC	5×10^7, twice	IV	SLEDAI, Scr, BUN, C4	Adverse event was not found	Yes
Li, 2016	Self-control	GC+CTX	III-IV type of LN or with type V	UC-MSC	1×10^6/kg-2×10^6/kg, 4 times	IV	SLEDAI, proteinuria, Scr, C3, C4	Two cases of fever, 2 cases of diarrhea, 1 case of vomiting, 1 case of pruritus	Yes
Qiu, 2016	Self-control	GC+CTX/MMF	Refractory SLE	UC-MSC	1×10^6/kg, once	IV	SLEDAI, proteinuria, C3	Adverse event was not found	Yes
Bai, 2017	Self-control	GC+CTX/MMF	Refractory SLE	UC-MSC	1×10^6/kg, 3-5 times	IV	SLEDAI, proteinuria, C3, C4	One patient with headache, nausea, and vomiting during each stem cell infusion	Yes
Wen, 2019	Self-control	GC +CTX/MMF/ LEF/HCQ	Refractory SLE	BM-MSC, UC-MSC	1×10^6/kg, once	IV	SLEDAI	—	Yes

Note: RCT: randomized controlled trail; BM-MSC: bone marrow-derived mesenchymal stem cells; UC-MSC: umbilical cord-derived mesenchymal stem cells; TAC: tacrolimus; GC: glucocorticoids; CTX: cyclophosphamide; IV: intravenous; MMF: mycophenolate mofetil; HCQ: hydroxychloroquine; LEF: leflunomide; SLE-DAI: systemic lupus erythematosus disease activity index; LN: lupus nephritis; T: MSC group; C: control group.

Zhou et al. Hindawi Stem Cells Intern 2020

MATHEC Maladies Auto-immunes et Thérapie Cellulaire

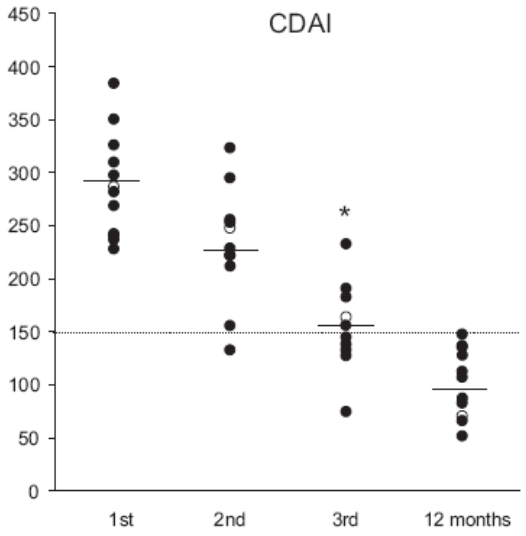
Lupus érythémateux systémique

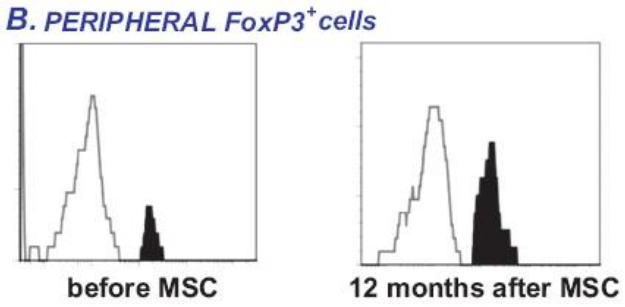
LUPUS ERYTHÉMATEUX SYSTÉMIQUE – Greffe de cellules souches mésenchymateuses allogéniques dérivées du cordon ombilical – Inclusions ouvertes.

- Patient *réfractaire aux traitements standards*
- *et dont* ***l'activité du Lupus est définie par un score SELENA-SLEDAI ≥ 6***
- Phase I - NCT03562065
- ***Pr D Farge, Hôpital Saint Louis***

CSM et MICI : traitement des fistules (Crohn)

- 12 refractory fistulising Crohn's patients
- 20 x 10^6 BM-derived MSC every 4 weeks
- 4 local injections
- sustained complete closure (n=7) or incomplete closure of fistula (n=3)
- reduction of Crohn's disease and perianal disease activity indexes at 12 month follow up
- Increase in peripheral blood CD25 FoxP3 Treg





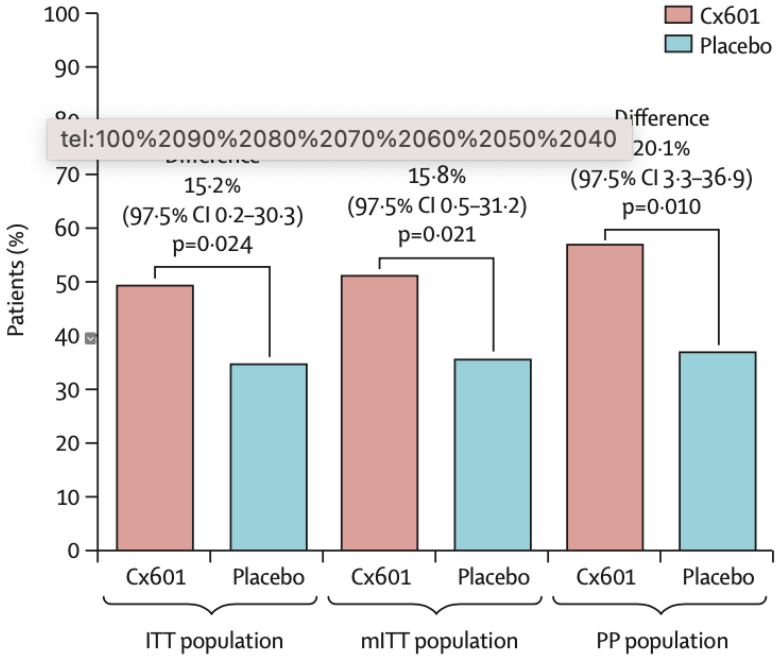
Gut 2011;**60**:788–798.

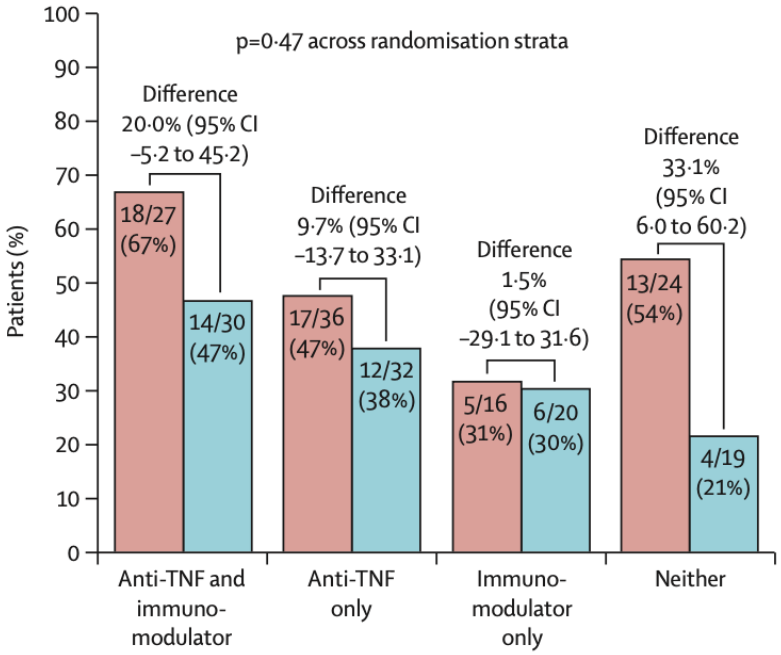
Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a phase 3 randomised, double-blind controlled trial

*Julián Panés, Damián García-Olmo, Gert Van Assche, Jean Frederic Colombel, Walter Reinisch, Daniel C Baumgart, Axel Dignass, Maria Nachury, Marc Ferrante, Lili Kazemi-Shirazi, Jean C Grimaud, Fernando de la Portilla, Eran Goldin, Marie Paule Richard, Anne Leselbaum, Silvio Danese, for the ADMIRE CD Study Group Collaborators**

>200 patients
Rémission à S24 (clinique + IRM)

	Cx601 (n=107)	Placebo (n=105)
Age (years)	39·0 (13·1)	37·6 (13·1)
Sex		
Male	60 (56%)	56 (53%)
Female	47 (44%)	49 (47%)
Ethnic origin		
Caucasian	100 (93%)	96 (91%)
Black	4 (4%)	1 (1%)
Other	0	1 (1%)
Missing	3 (3%)	7 (7%)
Weight (kg)	73·9 (15·0)	71·3 (14·9)
Crohn's disease duration (years)	12·1 (10·0)	11·3 (8·9)



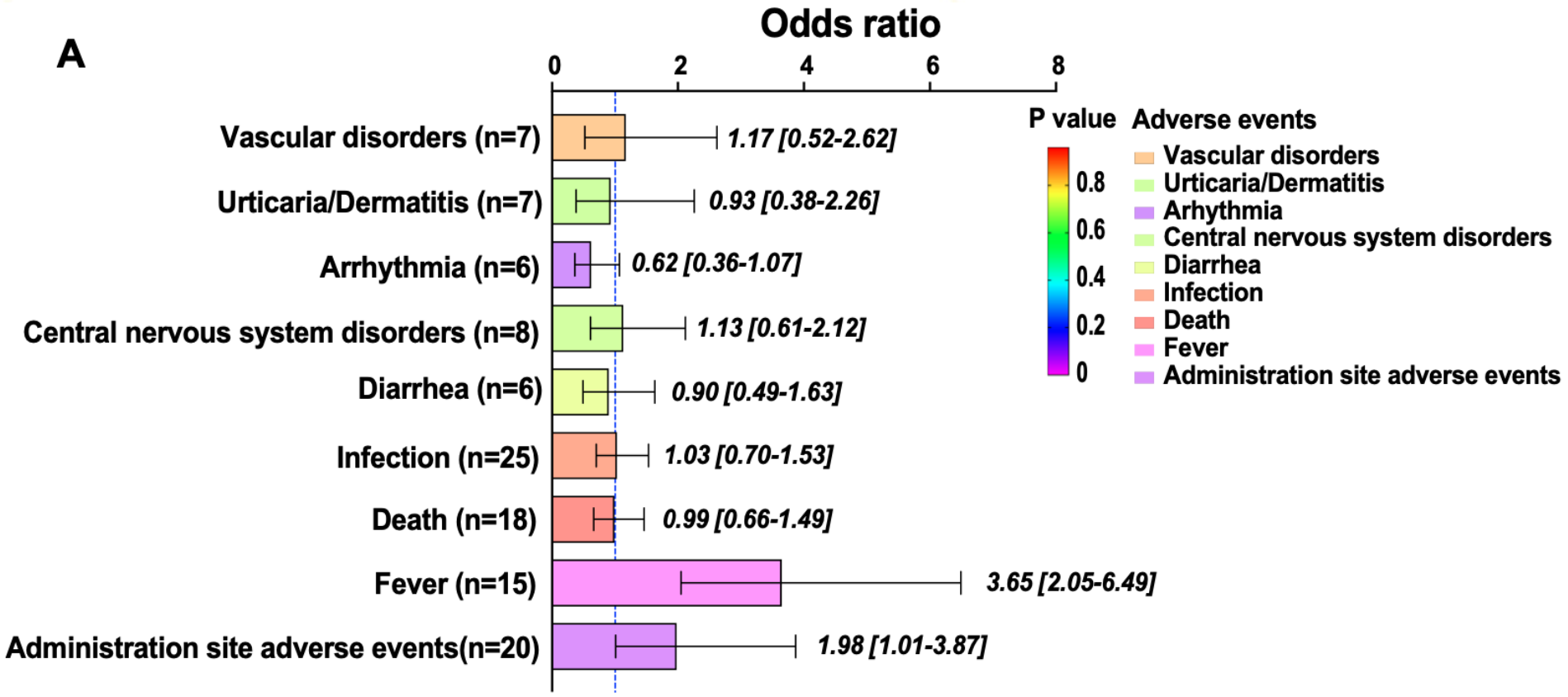


ALOFISEL, (darvadstrocel), thérapie cellulaire

AMM 2019 : **Intérêt clinique important uniquement dans le traitement des fistules périanales complexes de la maladie de Crohn en association à une biothérapie, lorsque ces fistules ont répondu de manière inadéquate à au moins une biothérapie et progrès thérapeutique mineur dans la stratégie thérapeutique**

HAS
HAUTE AUTORITÉ DE SANTÉ

Sécurité des thérapies basées sur les CSM



Wang et al. Stem Cell Res Ther 2021

CSM & MAI : questions posées en vue d'applications cliniques

Quel modèle pré-clinique ?

Dose et voie d'administration	Source tissulaire des CSM	Compatibilité des CSM	Pré-activation ? Thérapie a-cellulaire	Production & Cadre règlementaire
1. **Systémique** (PID) 2. **Locale** (UD) *Intranasale* *Intrathécale*	1. **Moelle Osseuse** 2. **Tissu Adipeux** 3. **Autres** (annexes placentaires)	1. **Autologue** Risque: altération de la niche 2. **Allogénique** Risque: rejet ?	**Pré-activation des CSM ?** **Vésicules extracellulaires:** - Exosomes - Microparticules	**Bio-réacteurs, banques de CSM** **Statut MTI/ATMP** GMP Plateformes (UTC, EFS)

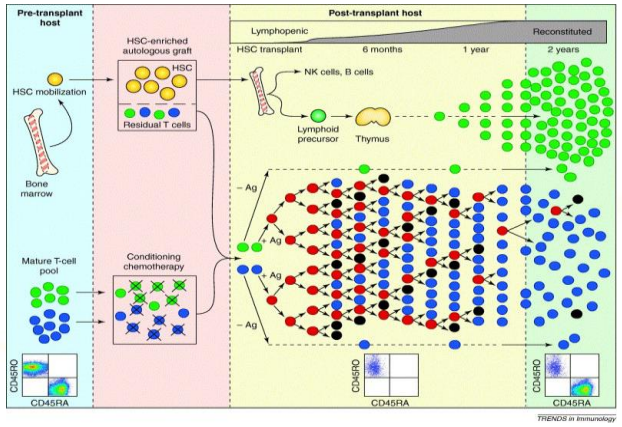
Thérapies Cellulaires et Sclérodermie Systémique: de l'autogreffe de moelle aux CSM

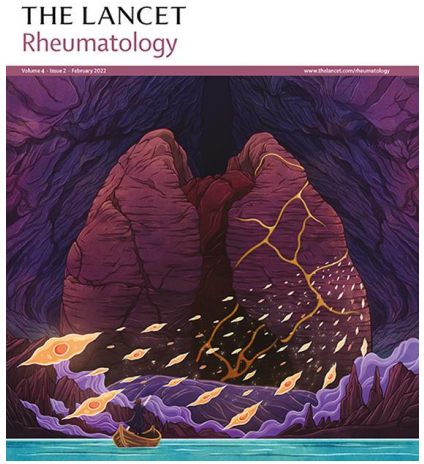
Autogreffe de CSH

- « Intensification » « Reset »
- Etudes cliniques [1,2,3]
- PNDS Sclérodermie
- PNDS Thérapie Cellulaire

Cellules Stromales Mésenchymateuses

- « Fine tuning », pas de conditionnement
- Propriétés trophiques
- Etudes précliniques
- Etudes cliniques préliminaires[4]

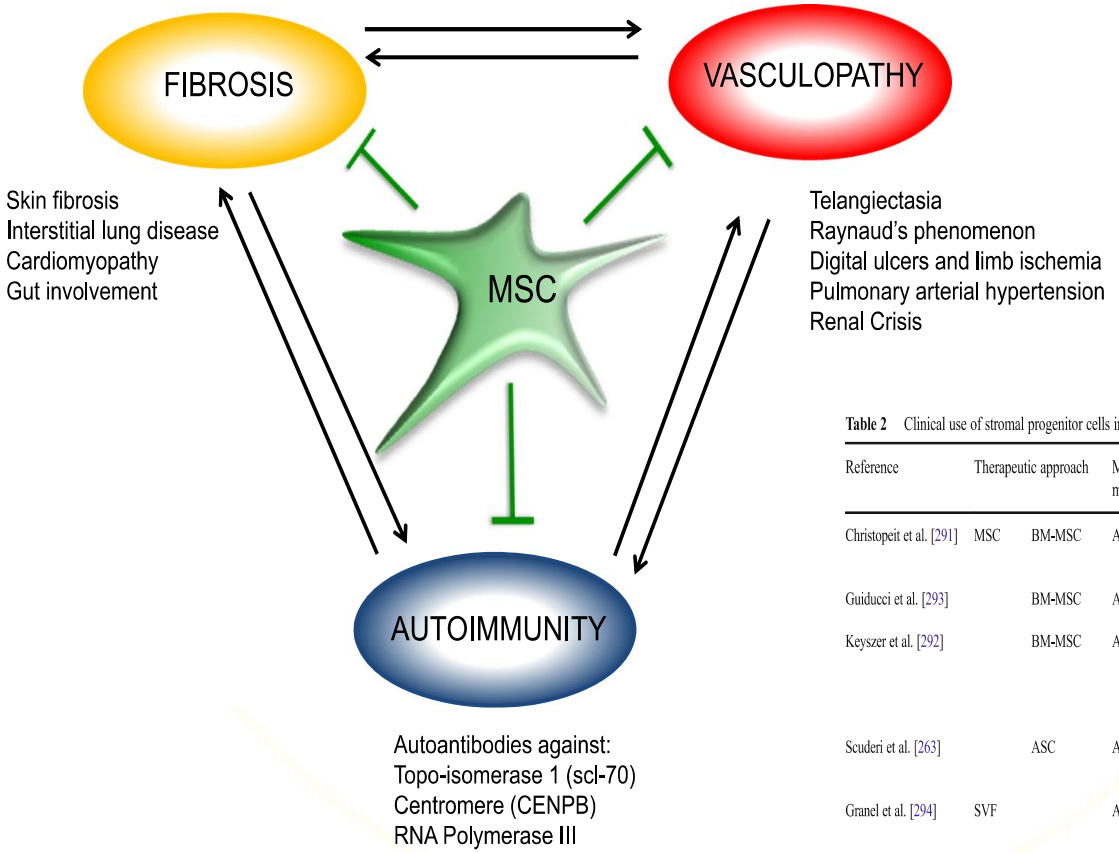




[1] Burt et al., Lancet 2011
[2] Van Laar et al. JAMA 2014
[3] Sullivan et al. NEJM 2018

[4] Farge et al. Lancet Rheumatol 2022

CSM dans la ScS : une approche globale



Del Papa et al., Cell Transplant 2015

Table 2 Clinical use of stromal progenitor cells in patients with systemic sclerosis: state of the art

Reference	Therapeutic approach		MHC matching	Route	No of patients	Sex	Age	Phenotype of scleroderma patients	Outcome	Adverse events
Christopeit et al. [291]	MSC	BM-MSC	Allogeneic	Systemic (IV)	1	F	41	✓ Skin fibrosis ✓ Vasculopathy (DU)	✓ Healing of DU ✓ Improved tcpO2 ✓ Improved mRSS (−16)	None
Guiducci et al. [293]		BM-MSC	Autologous	Systemic (IV)	1	F	34	✓ Vasculopathy (limb acute ischemia)	✓ Skin healing ✓ Limb revascularization	None
Keyszer et al. [292]		BM-MSC	Allogeneic	Systemic (IV)	5#	M (3/5)	39 ± 10	✓ Skin fibrosis (5/5) ✓ ILD (4/5) ✓ Vasculopathy (5/5) ✓ Myositis (2/5) ✓ Cardiopathy (4/5)	✓ Healing of DU ✓ Improved mRSS (3/5) ✓ Improved myositis ✓ No ILD improvement	✓ Minor respiratory tract infection (4/5)
Scuderi et al. [263]		ASC	Autologous	Local (skin), hyaluronic acid scaffold	6	F (4/6)	28 ± 8	✓ Skin fibrosis (localized scleroderma)	✓ Improved scleroderma (5/6)	None
Granel et al. [294]	SVF		Autologous	Local (fingers)	12	F (12/12)	54 ± 10	✓ Skin fibrosis (11/12) ✓ Vasculopathy (RP, DU) (12/12)	✓ Improved mRSS (−2,4) ✓ Functional scores ✓ Doppler improvement ✓ Quality of life scores	✓ Pain* ✓ Paraesthesia$

F female, *M* male, *RP* Raynaud's phenomenon, *DU* digital ulcers, *ILD* interstitial lung disease, *BM-MSC* bone marrow-derived mesenchymal stem cell, *SVF* stromal vascular fraction, *ASC* adipose-derived MSC, *MHC* major histocompatibility complex, *IV* intravenous, *mRSS* modified Rodnan skin score, *tcpO2* transcutaneous partial oxygen pressure

Christopeit et al., Leukemia 2008

Maria et al, CRAI 2016

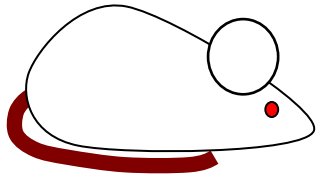
CSM & ScS : modèles précliniques d'étude

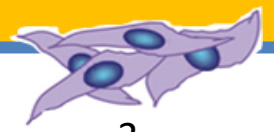
Bléomycine

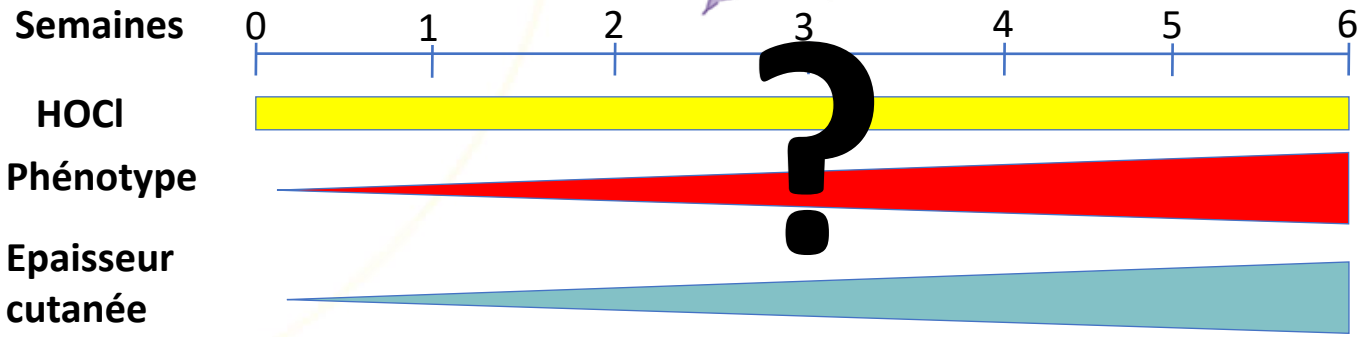
« Génétiques »

Acide Hypochloreux (ScS-HOCl)

1. Fibrose Multi-Organes
2. Microangiopathie
3. Auto-immunité







Servettaz et al., JI 2009
Servettaz et al., Am J Pathol 2010
Kavian et al., A & R 2010
Kavian et al., A & R 2012
Marut et al., J Invest Dermatol 2012
Marut et al., Arthritis 2013
Marut et al., ART 2013
Kavian et al., A & R 2015
Kavian et al., JI 2016
Morin et al., JI 2016
Morin et al., Free Radic Biol Med 2017

Hua-Huy et al., J Breath Res 2015
Bei et al., Exp Lung Res 2016

Bagnato et al., Rheumatology 2013
Bagnato et al., ART 2013 et 2014
Bagnato et al., Vascul Pharmacol 2015

Racker et al. Exp Dermatol 2016

Sanges et al., Frontiers in Immunol 2017

Lescoat et al., Biochem Pharmacol 2020

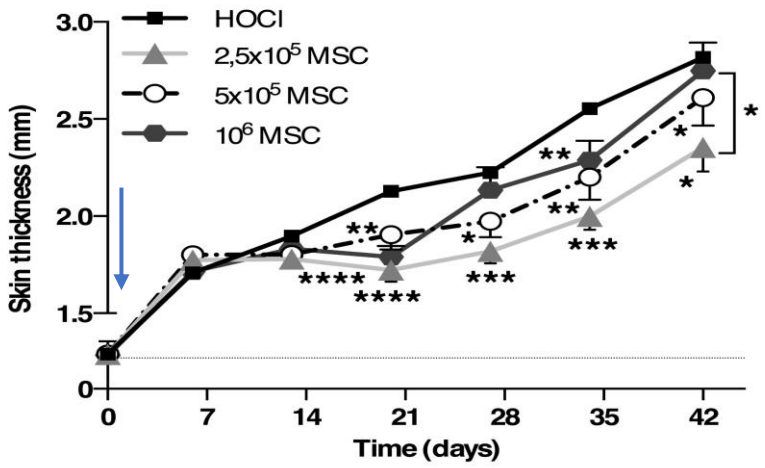
Xia et al., Oncol Lett 2018
Meng et al. Frontiers Immunol 2019

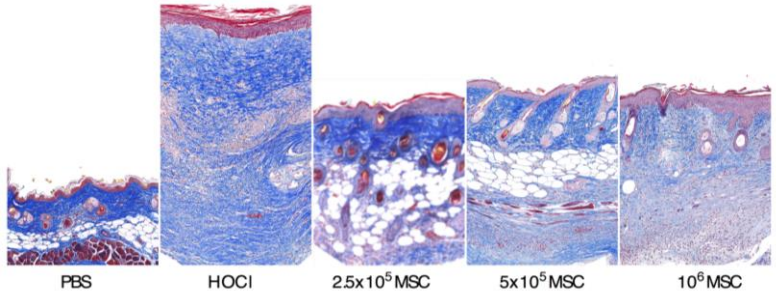
Maria et al., A & R 2015
Maria et al., A & R 2016
Maria et al., J Autoimmunity 2016
Maria et al., Frontiers in Immunol 2018
Maria et al., Frontiers in Immunol 2019

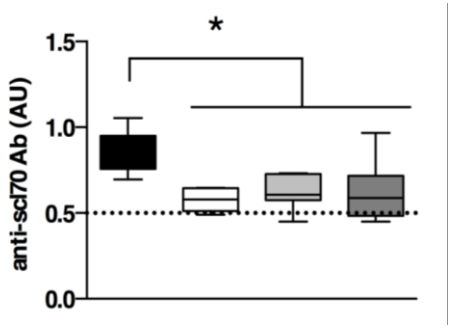
Rozier et al., J Autoimmunity 2021
Rozier et al., Cells 2021
Rozier et al., IJMS 2021

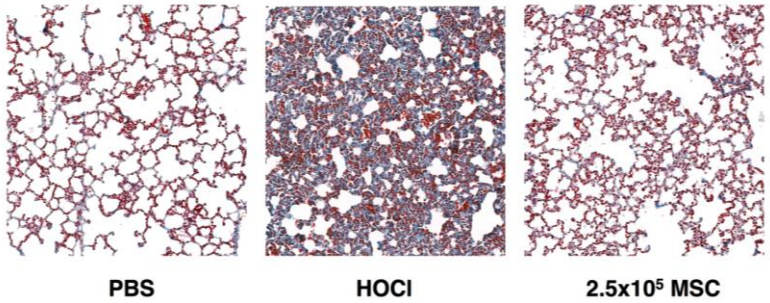
Jin IJSC 2021

CSM & ScS : preuve de concept préclinique



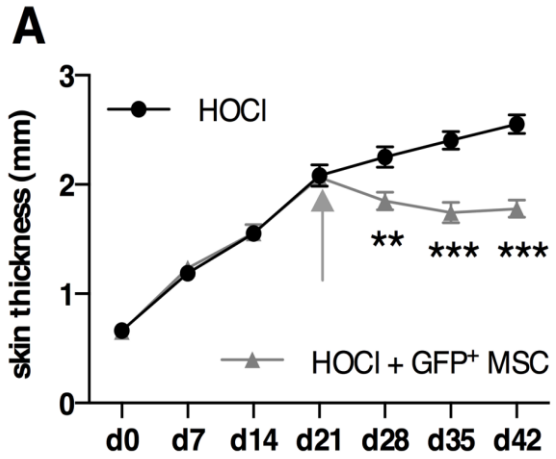


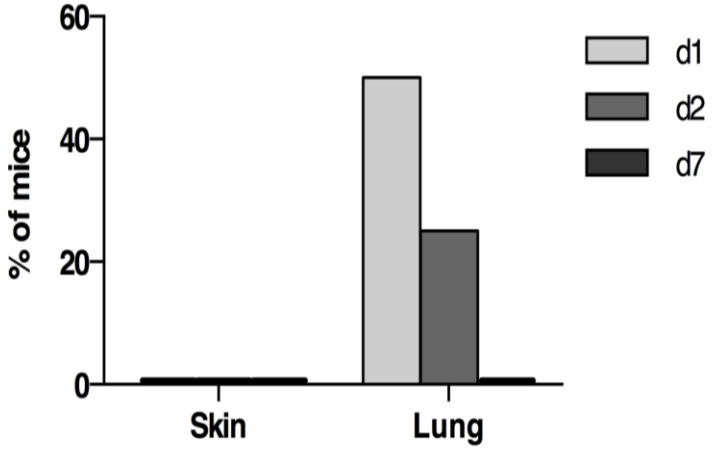




→ *<u>Préventif</u>: CSM à J0 ou <u>curatif:</u> CSM à J21, voire J42*
→ *Effet dose « inversé » : 2.5x10⁵ CSM*
→ *Réduction de la fibrose cutanée & pulmonaire*
→ *Réduction des auto-anticorps et du stress oxydant*

CSM & ScS : mécanismes d'action: bio-distribution





Pas de migration des CSM

=

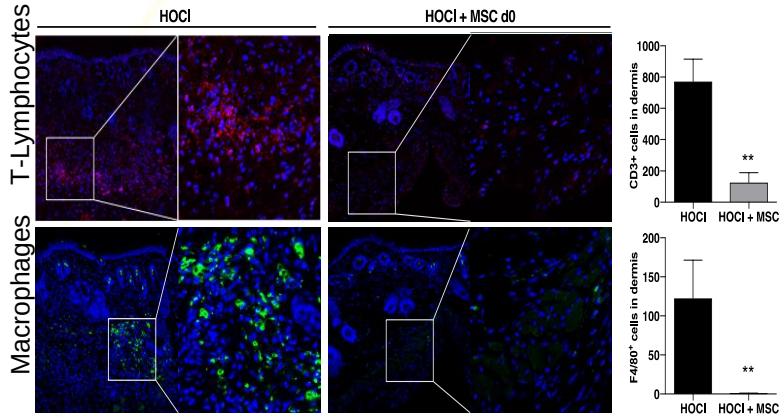
Mécanisme paracrine/exocrine d'action

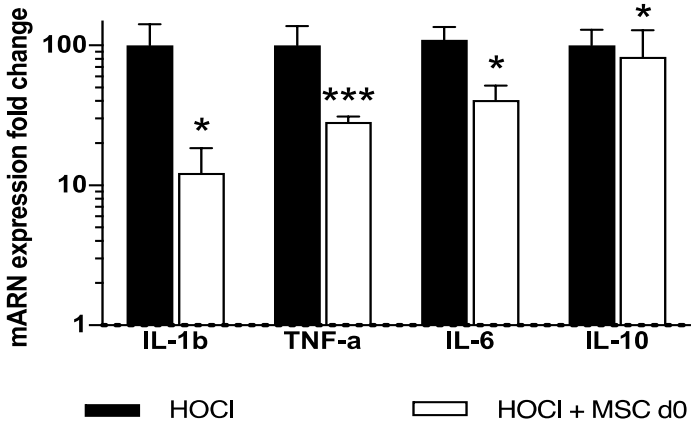
=

« Kiss n Go »: secretome

Maria et al., Reply to Cipriani, A&R, 2016

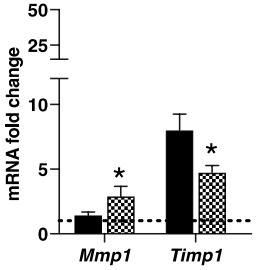
Principaux effets des MSC: pléïotropiques

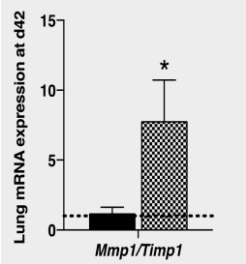


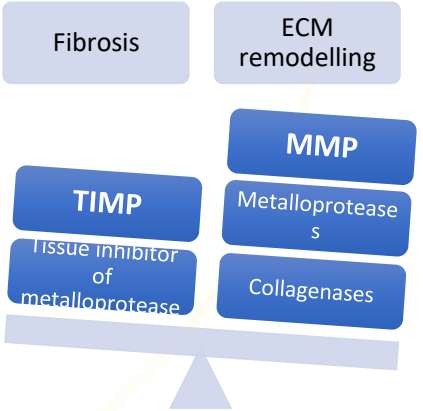


Immunosuppression

Maria ATJ et al., Frontiers in Immunol 2018

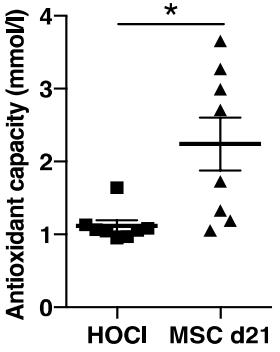


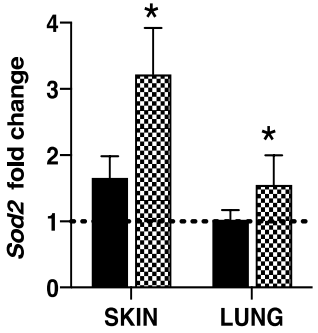


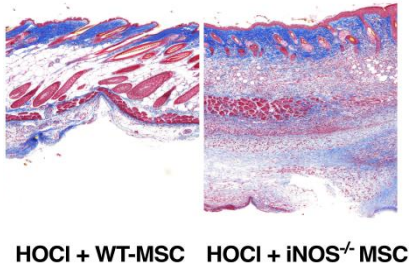


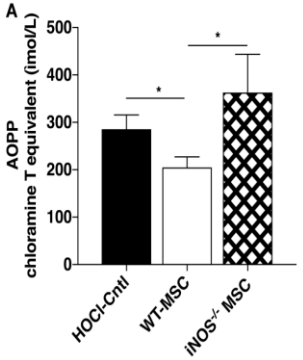
Remodelage MEC

Maria ATJ et al., A&R, 2016
Maria ATJ et al., Frontiers in Immunol 2019









Anti-oxydant

Maria et al. J Autoimmunity 2016

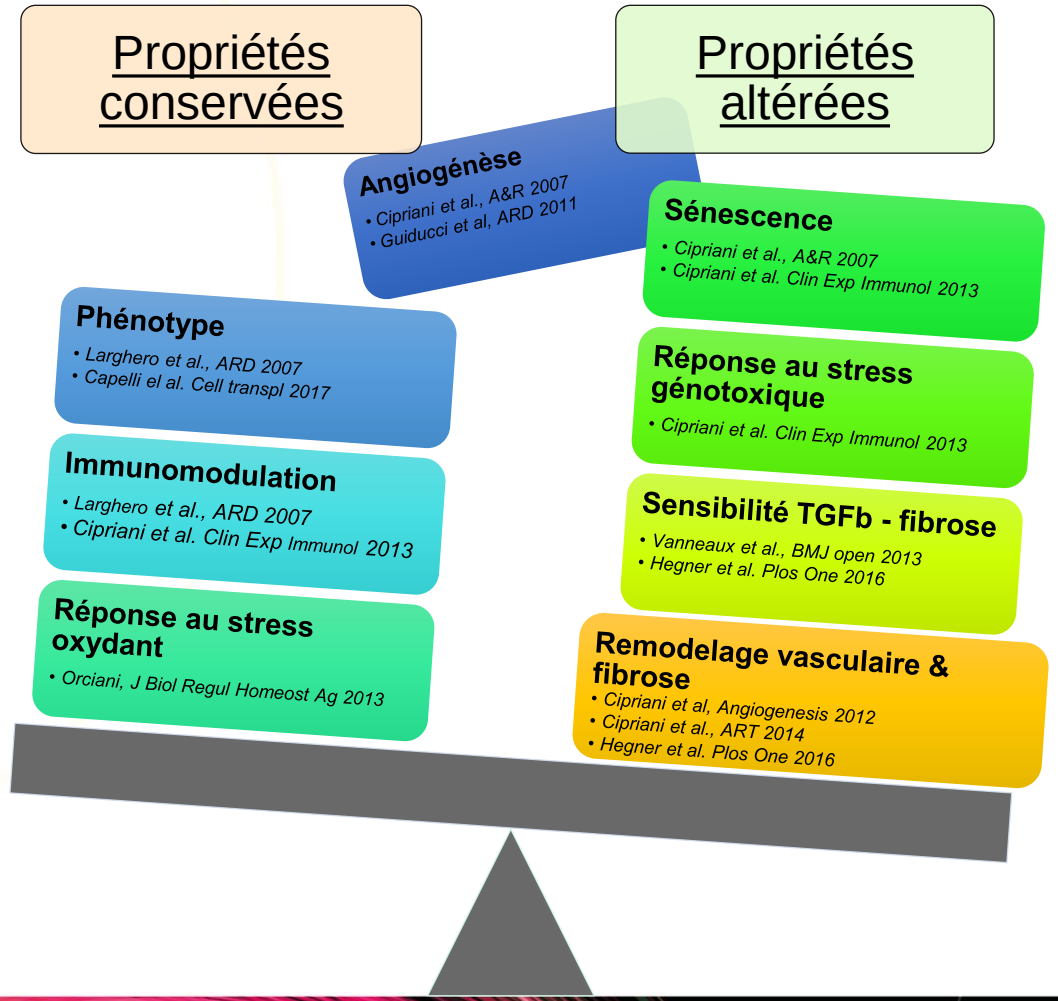
Quelle compatibilité antigénique ?

AUTOLOGUE

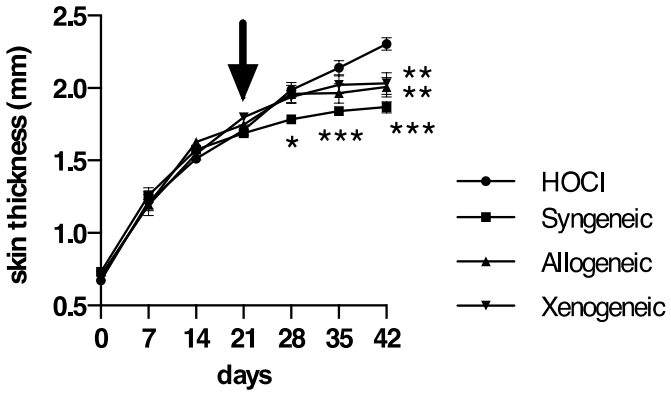
- Facilité de procédure
- Pas de rejet
- **Altérations liées à la pathologie ?**

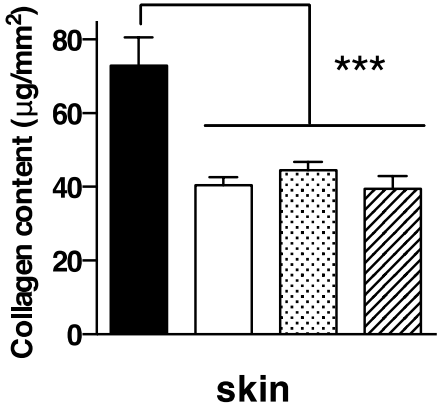
ALLOGENIQUE

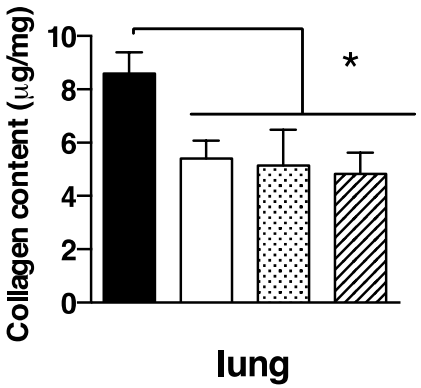
- Réponse immunitaire
- Quelle compatibilité ?
- Donneur sain universel
- Facilité de développement (coût)

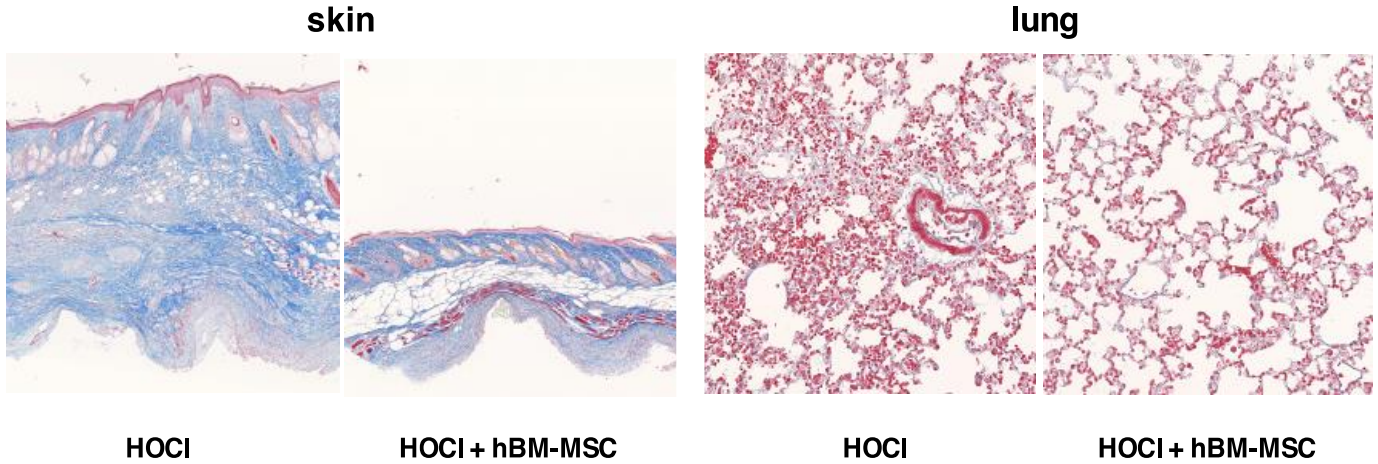


Compatibilité antigénique: approches syn-, allo-, et xénogéniques







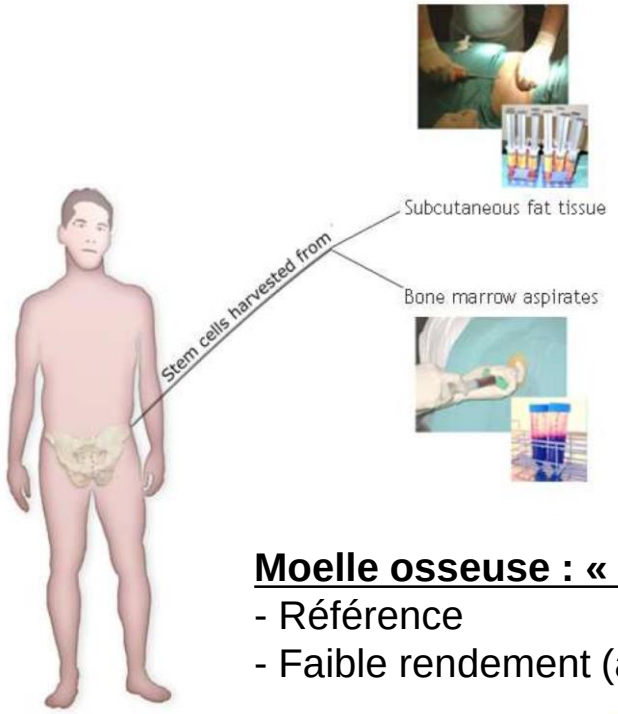


→ **Effets similaires quelle que soit la compatibilité antigénique**

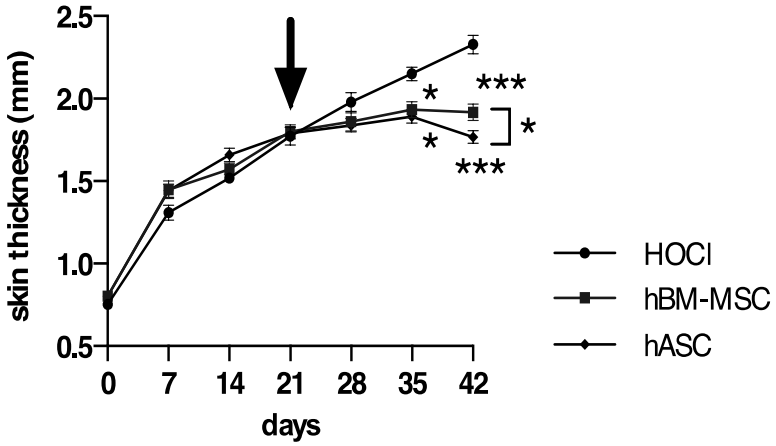
Maria et al., J Autoimmun 2016

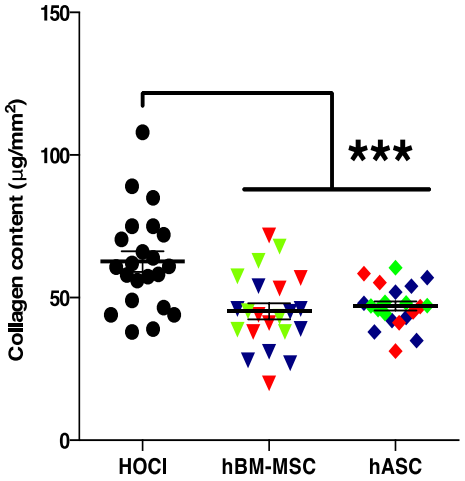
Origine tissulaire: ASC vs BM-MSC

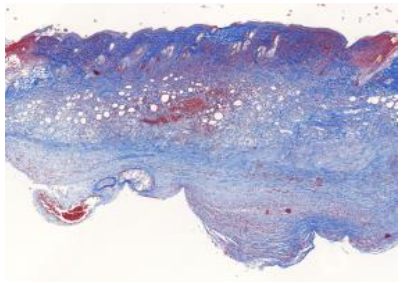
Tissu adipeux : « ASC »
- Rendement supérieur (x10,000)
- Propriétés fonctionnelles accrues ?



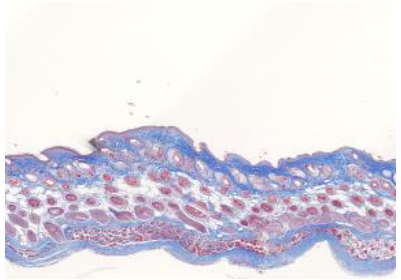
Moelle osseuse : « BM-MSC »
- Référence
- Faible rendement (âge)



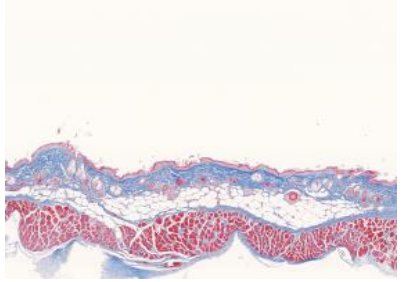




HOCl



hBM-MSC

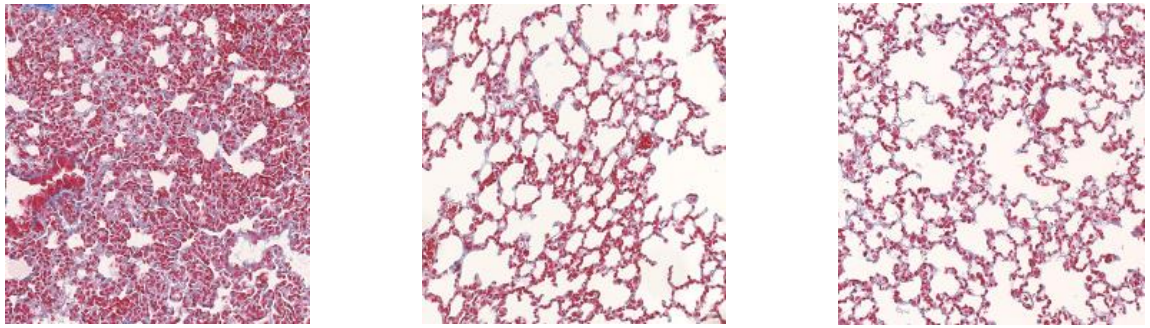


hASC

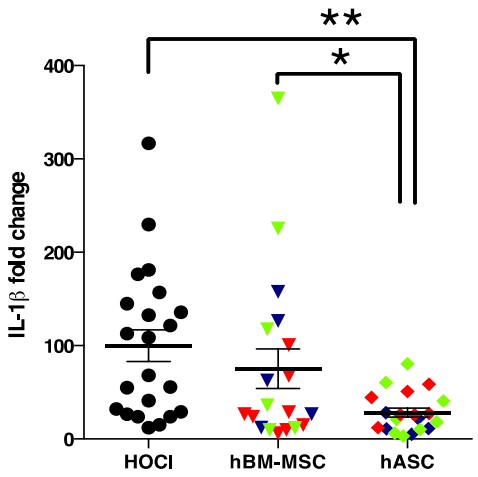
→ Effet antifibrotique comparable sur la peau

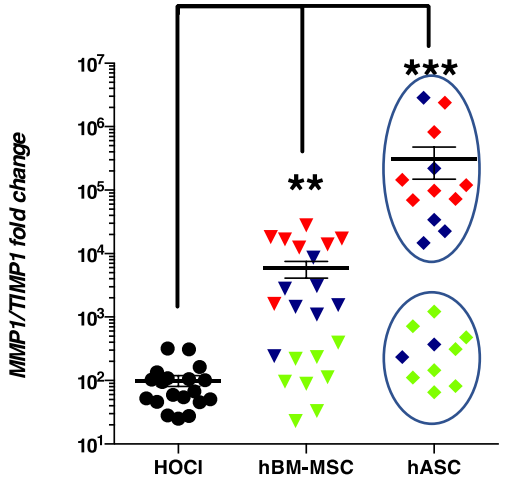
Maria et al., J Autoimmun 2016

Origine tissulaire: ASC vs BM-MSC



HOCl hBM-MSC hASC





Effet donneur

→ **Effet immunosuppresseurs et pro-remodelage supérieurs des ASC**

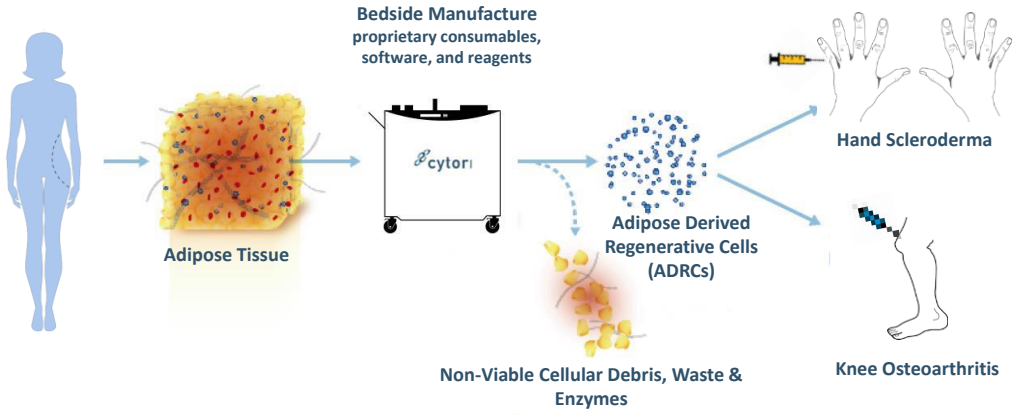
Maria et al., J Autoimmun 2016

Tissu Adipeux: SVF & ASC dans la ScS

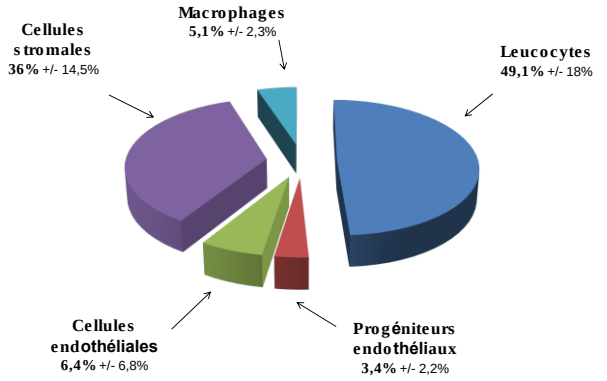
EXTENDED REPORT

Safety, tolerability and potential efficacy of injection of autologous adipose-derived stromal vascular fraction in the fingers of patients with systemic sclerosis: an open-label phase I trial

Brigitte Granel,[1,2] Aurélie Daumas,[1] Elisabeth Jouve,[3] Jean-Robert Harlé,[1] Pierre-Sébastien Nguyen,[4] Christian Chabannon,[5] Nathalie Colavolpe,[6] Jean-Charles Reynier,[7] Romain Truillet,[3] Stéphanie Mallet,[8] Antoine Baiada,[4] Dominique Casanova,[4] Laurent Giraudo,[9] Laurent Arnaud,[10] Julie Veran,[9] Florence Sabatier,[2,9,10] Guy Magalon[4,9]



Caractérisation de la FVS



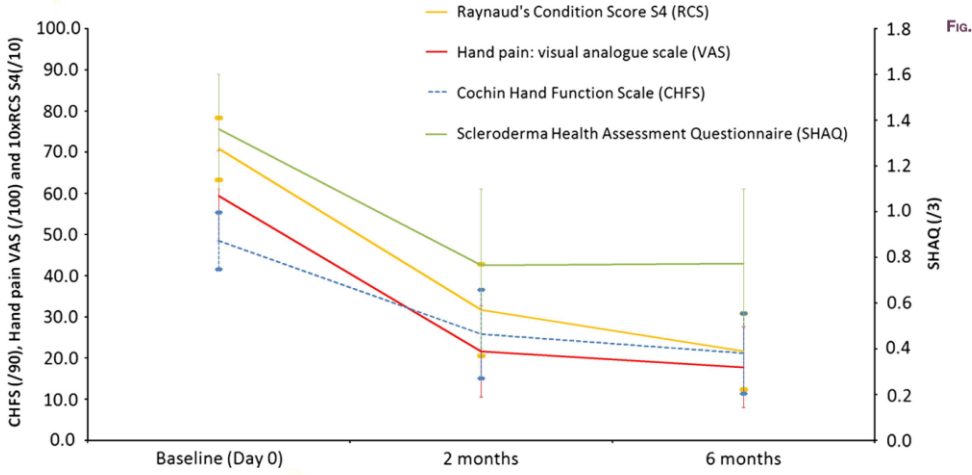
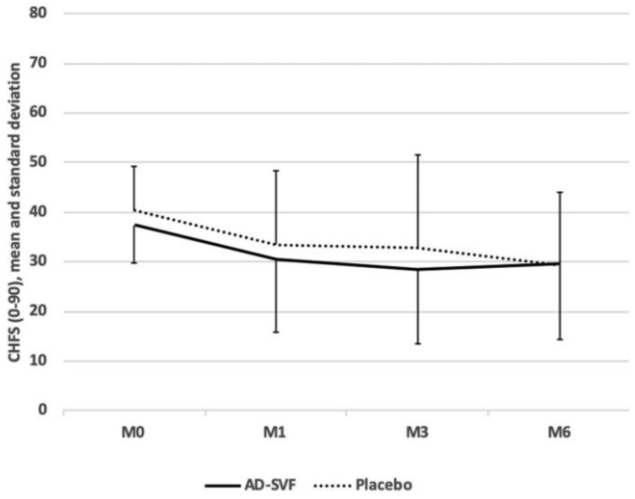


Fig. 3 Cochin Hand Function Scale score outcome



SCLERADEC: 12 femmes
Injections locales de SVF autologue (contenant CSM)

Granel et al. Rheumatology 2021

Hôpitaux de Toulouse

INJECTION DE CELLULES SOUCHES MESENCHYMATEUSES AUTOLOGUES ISSUES DE TISSU ADIPEUX DANS LA PRISE EN CHARGE DES ULCERES DIGITAUX DE LA SCLERODERMIE SYSTEMIQUE
ESSAI DE PHASE 2

ETUDE ADUSE

Pr G Pugnet, Toulouse

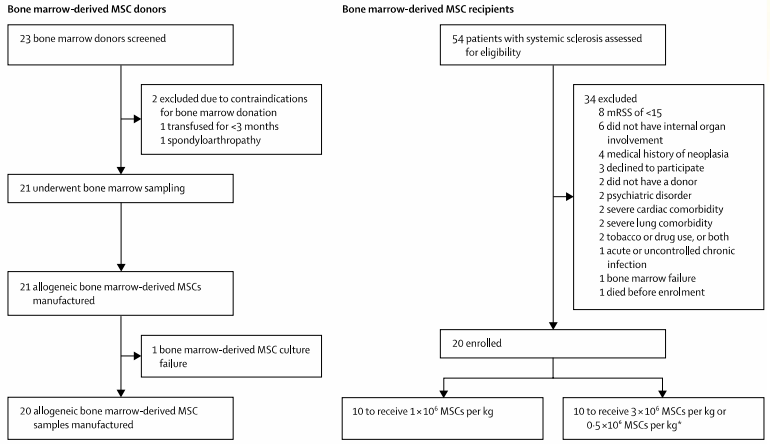
CSM & ScS : Essai clinique pilote

Safety and preliminary efficacy of allogeneic bone marrow-derived multipotent mesenchymal stromal cells for systemic sclerosis: a single-centre, open-label, dose-escalation, proof-of-concept, phase 1/2 study

Dominique Farge, Séverine Loisel, Matthieu Resche-Rigon, Pauline Lansiaux, Ines Colmegna, David Langlais, Catney Charles, Grégory Pugnet, Alexandre Thibault Jacques Maria, Emmanuel Chatelus, Thierry Martin, Eric Hachulla, Vissal David Kheav, Nathalie C Lambert, HanChen Wang, David Michonneau, Christophe Martinaud, Luc Sensebé, Audrey Cras†, Karin Tarte†*

www.thelancet.com/rheumatology **Published online January 5, 2022 https://doi.org/10.1016/S2665-9913(21)00326-X**

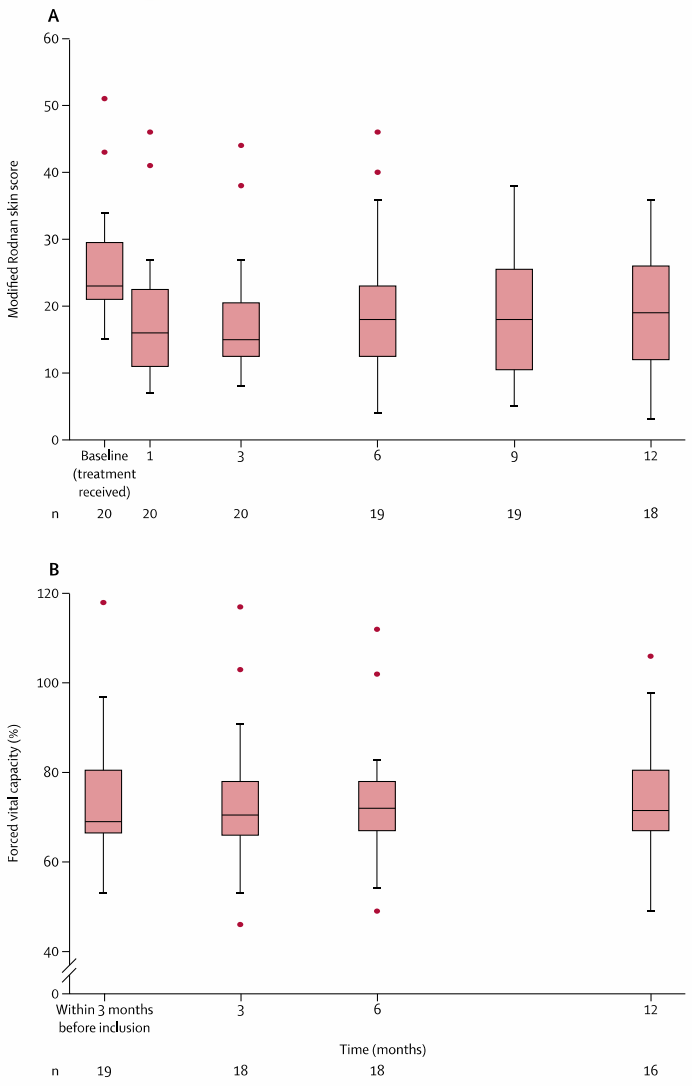
THE LANCET
Rheumatology

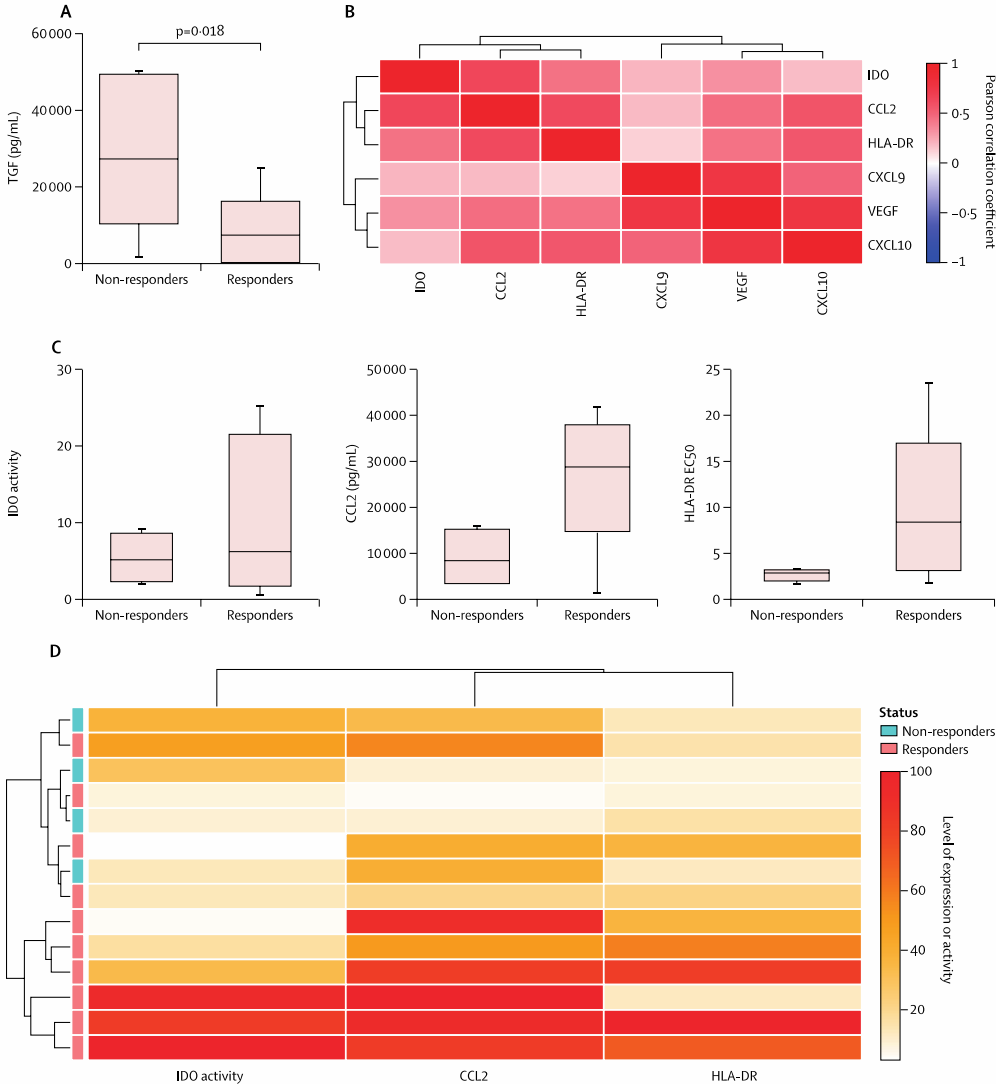


Findings Between March 24, 2014, and Jan 6, 2020, 20 cisgender individuals (13 women and seven men) with severe diffuse systemic sclerosis were enrolled. All 20 patients were included in the primary outcome analysis. No infusion-related severe adverse events and three infusion-related adverse events occurred in the first 10 days after treatment; one patient had grade 1 flushing and another patient had grade 1 nausea and grade 2 asthenia. After ten days and up to a median follow-up of 24·1 months (IQR 20·8–24·5), 36 non-treatment-related severe adverse events in 14 (70%) patients and no treatment-related adverse event were reported.

	Participants (n=20)
Age, years	47 (36–57)
Gender	
Female	13 (65%)
Male	7 (35%)
Disease duration, years	6·9 (4·6–10·0)
Diffuse systemic sclerosis	20 (100%)
Cutaneous and juxta-articular involvement	
Digital ulcers	9 (45%)
Raynaud's phenomenon	16 (80%)
Modified Rodnan skin score†	23 (21–29)
Tendon friction rub	16/18 (89%)
Pulmonary function	
Rales	15 (75%)
Interstitial lung disease§	20 (100%)
Abnormal chest x-ray	17/19 (89%)
Abnormal high-resolution CT	19/19 (100%)
Partial pressure of oxygen at room air, mmHg	100 (92–113; 19 [95%])*
Pulmonary function tests	
Percent predicted vital capacity	70·5% (63·0–78·8; 18 [90%])*
Percent predicted total lung capacity	77% (72·5–95·5; 19 [95%])*
Percent predicted forced vital capacity	69% (66·5–80·5; 19 [95%])*
Percent predicted DLCO	39·8% (34·7–50; 19 [95%])*
Anti-Scl70 antibody positive	16 (80%)
Anti-centromere antibody positive	0 (0%)
Anti-RNP antibody positive	2 (10%)
Anti-RNA polymerase III antibody positive	2 (10%)

CSM & ScS : Essai clinique pilote: données préliminaires





Facteurs prédictifs de non réponse?

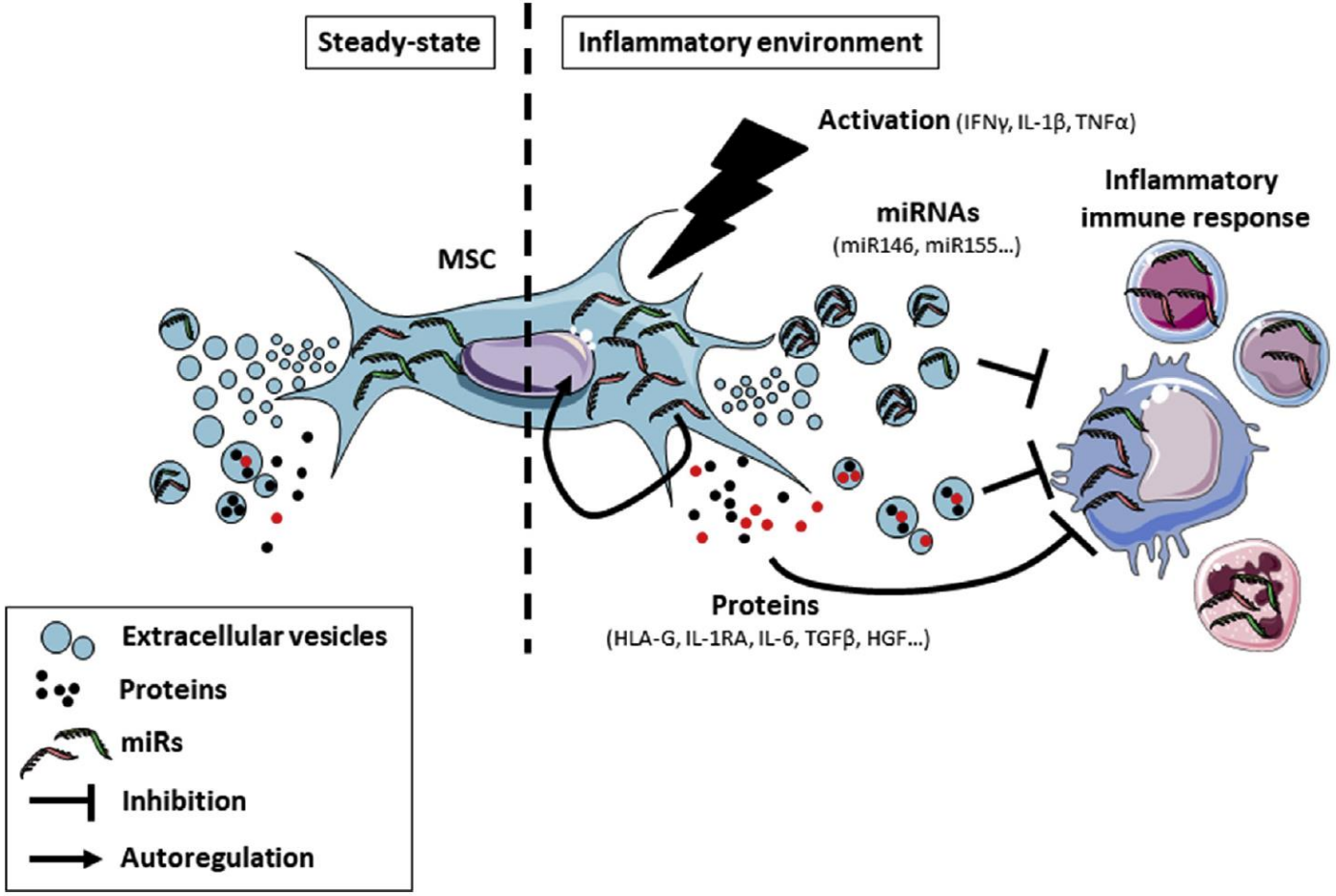
<u>Receveur</u>:
High TGFb

<u>Donneur</u>:
Low CCL2
Low IDO
Low HLA-DR

Potency Assay Matching

Perspectives au-delà des CSM: Vers une thérapie acellulaire ?

Y.-M. Pers et al. / Biochimie xxx (2018) 1–10



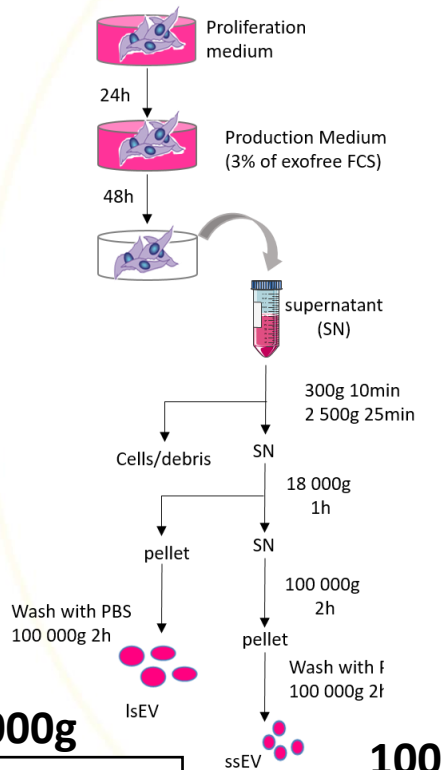
L'effet thérapeutique des CSM est médié par la sécrétion de vésicules extracellulaires contenant les molécules solubles d'intérêt (protéines, microARN…)

soluble

<u>Large-sized EV</u>
Enriched in microvesicles
100 à 1000 nm
Membrane budding

<u>Small-sized EV</u>
Enriched in exosomes
30 à 150 nm
Endosomal compartment

Vésicules Extracellulaires (EV-MSC)



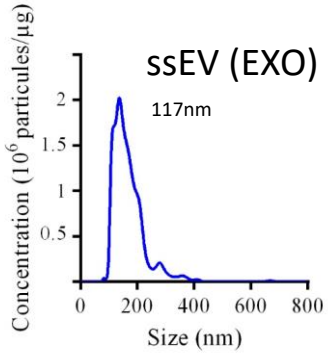
18 000g

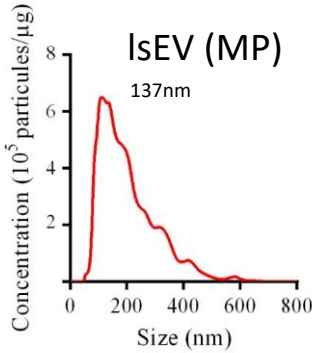
lsEV
≥200nm

100 000g

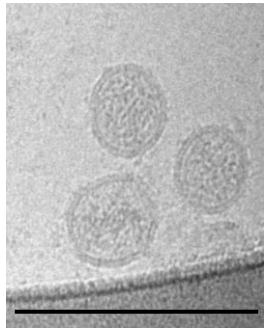
ssEV
≤200nm

Nanotracking analysis (NTA)

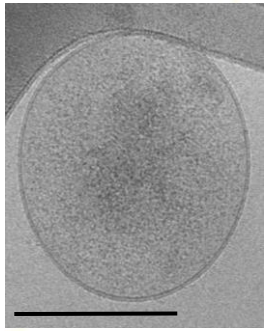




Cryo-TEM

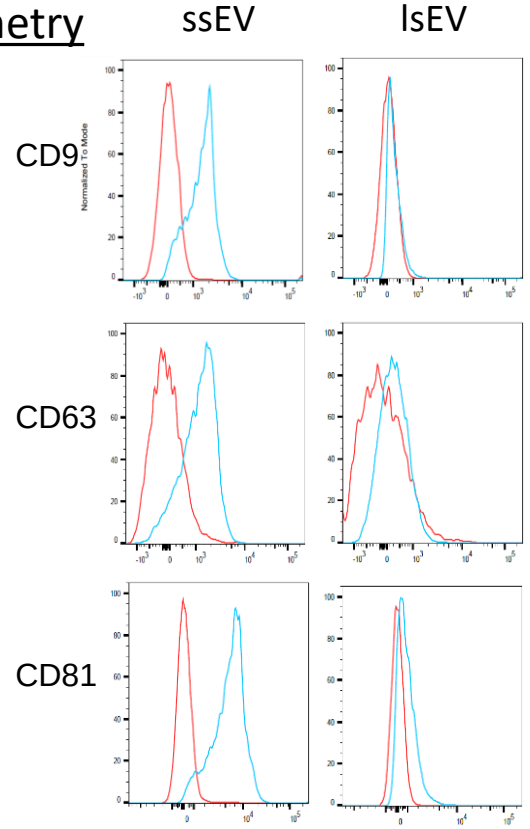


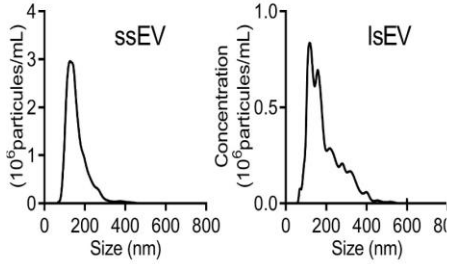
ssEV

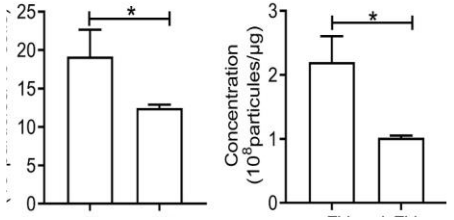


lsEV

Cytometry

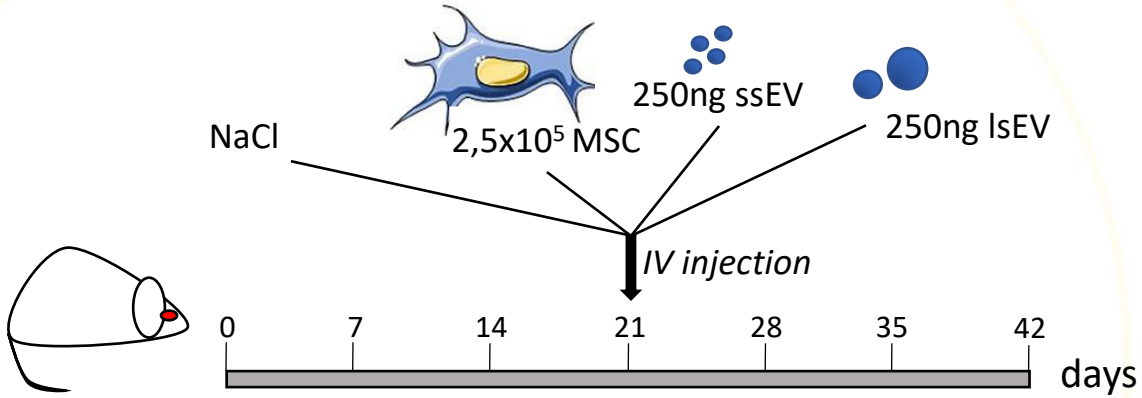




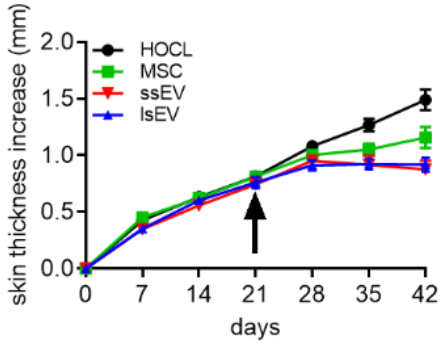


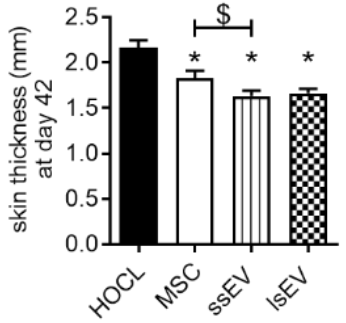
Endosomal markers (ssEV: exosomes)

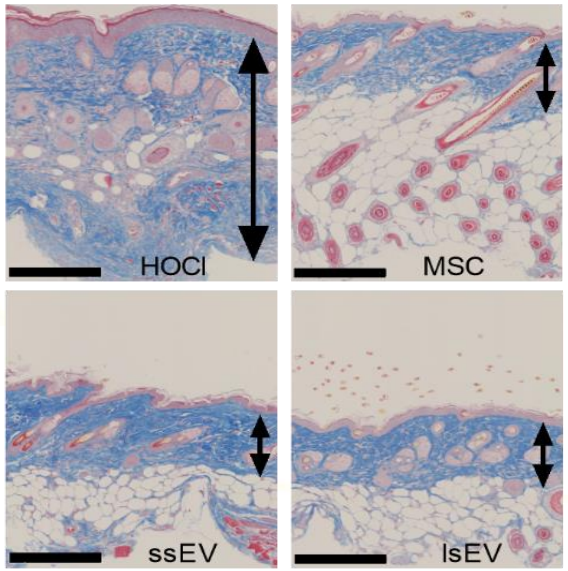
Les EV sont aussi efficaces que les MSC

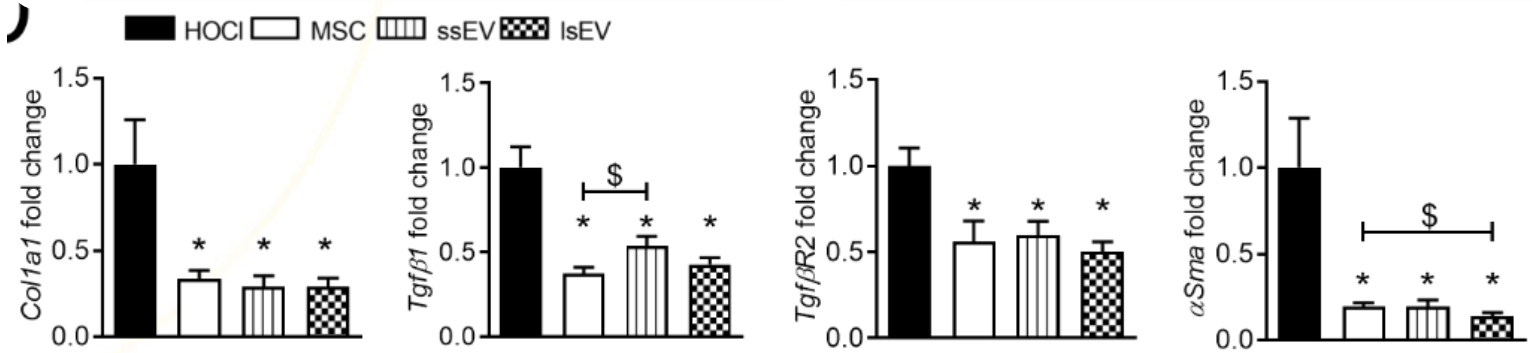


Clinical effect



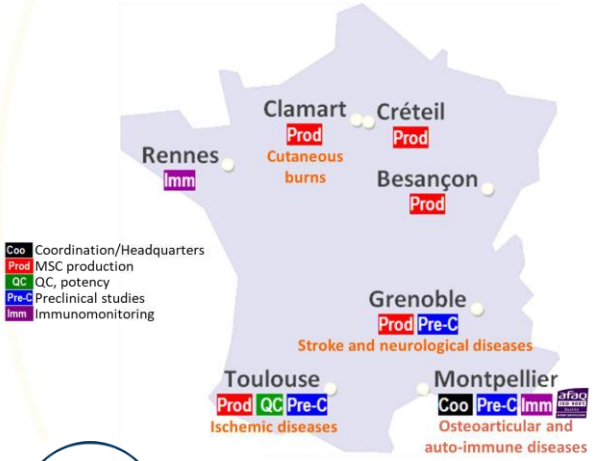






Rozier et al, Cells 2021

Des CSM-GMP aux EV de grade clinique



- 7 sites
- 57 research scientists (excluding clinical staff)
- 11 technological platforms :
  - Non clinical (3)
  - Production ATMP (5)
  - Quality control/safety/potency (1)
  - Immunomonitoring (2)
- 10 gouvernemental research organisations involved
- 18 National and European clinical programs running in 2020

Coordination : Université de Montpellier
Coordinator : Christian Jorgensen
Project manager : Séverine Kremer

EFS
ÉTABLISSEMENT FRANÇAIS DU SANG

ECell France
For Regenerative Medicine

INTERNATIONAL SOCIETY for EXTRACELLULAR VESICLES

Advanced Drug Delivery Reviews 179 (2021) 114001

Contents lists available at ScienceDirect

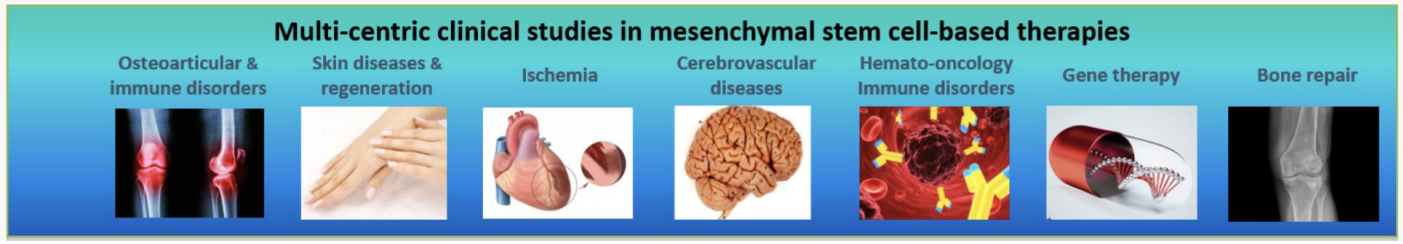
Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/adr

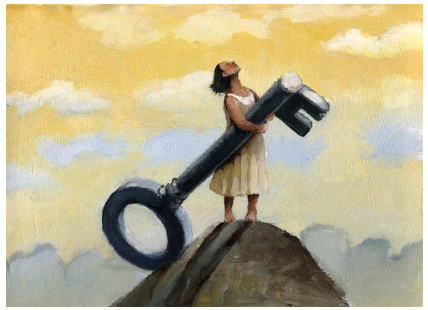
Development of extracellular vesicle-based medicinal products: A position paper of the group "Extracellular Vesicle translatiOn to clinicaL perspectiVEs – EVOLVE France"

Amanda K.A. Silva [a,*], Marie Morille [b], Max Piffoux [a,c,d], Surendar Arumugam [a], Phlippe Mauduit [c,e], Jérôme Larghero [f,g], Arnaud Bianchi [h], Kelly Aubertin [a], Olivier Blanc-Brude [i], Danièle Noël [j,k], Emilie Velot [h,l], Célia Ravel [m,n], Céline Elie-Caille [o], Anna Sebbagh [a], Chantal Boulanger [i], Claire Wilhelm [p], Gabriel Rahmi [q,r], Isabelle Raymond-Letron [s,t], Kondareddy Cherukula [a], Tristan Montier [u,v], Christophe Martinaud [c,k,w], Jean-Marie Bach [x], Olivier Favre-Bulle [y], Jolanda Spadavecchia [z], Christian Jorgensen [j,k], Philippe Menasché [i,aa], Clotilde Aussel [c,ab], Joël Chopineau [b], Mathilde Mosser [x], Matti Ullah [a], Nicolas Sailliet [ac], Nathalie Luciani [a], Noëlle Mathieu [ad], Pierre-Emmanuel Rautou [ae], Sophie Brouard [ac], Wilfrid Boireau [o], Sébastien Jauliac [af], Marianne Dedier [c,ab], Jean-Hugues Trouvin [ag], Florence Gazeau [a], Marina Trouillas [c,k,ab], Juliette Peltzer [c,k,ab], Antoine Monsel [ah,ai], Sébastien Banzet [c,k,ab,*]

ATMP Advanced Therapy Medicinal Products



Messages clés

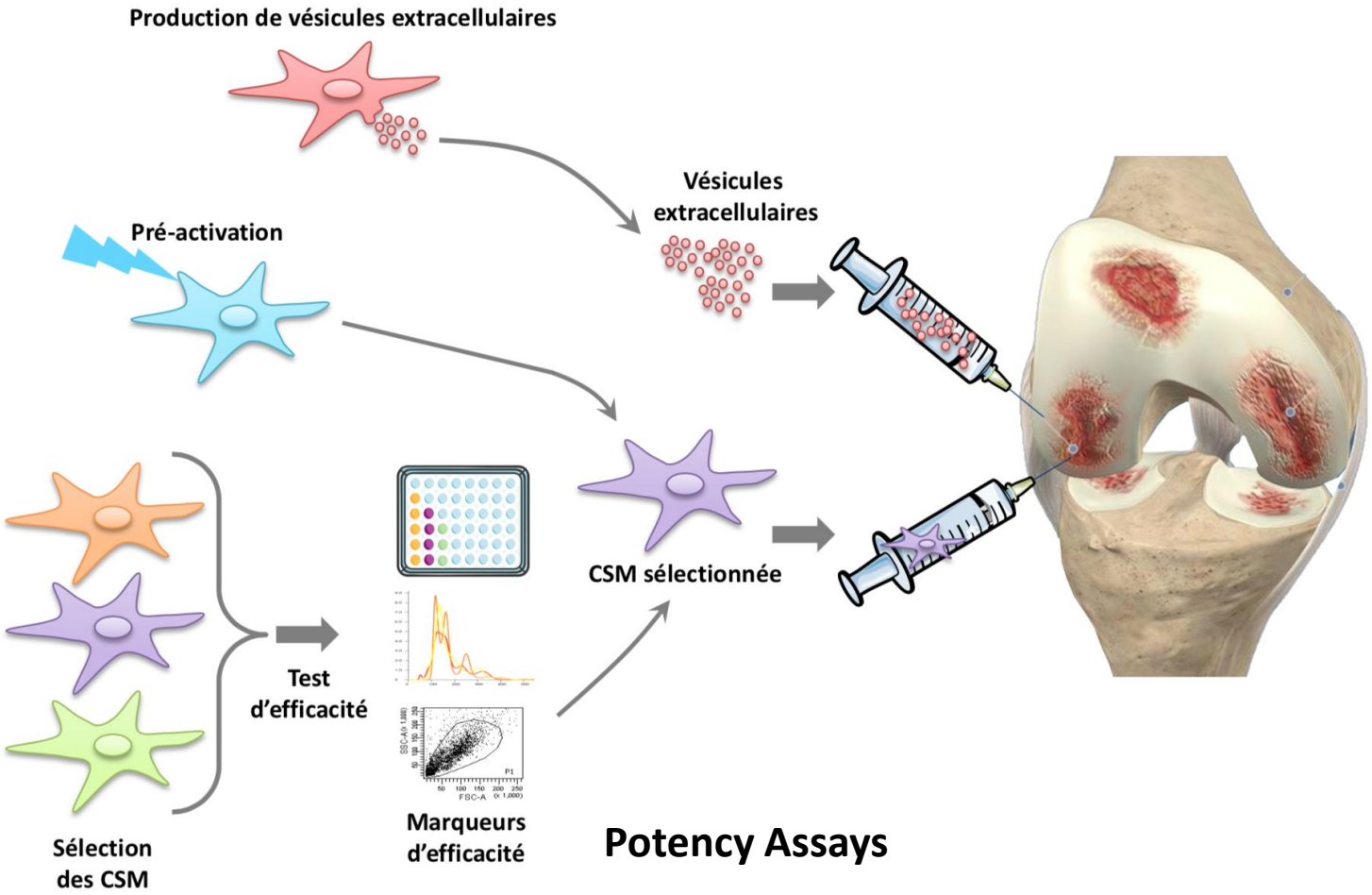


Cellules Stromales Mésenchymateuses:

- *Multiples applications dans les pathologies inflammatoires / auto-immunes*
- Effets pléïotropes, immunomodulation et rôles trophiques / antifibrotiques
- Effets indépendants de la persistance des CSM (kiss n go)
- Pharmacologie spécifique
- Sources tissulaires multiples: ASC et UC-MSC
- Approches allogéniques (banques de CSM)
- Thérapies acellulaires, basées sur les vésicules extracellulaires
- Importances des études pré-cliniques, **mais besoin d'ERC phase 3 +++**
- Développement grade clinique: cadre règlementaire spécifique (GMP, MTI)

En résumé: perspectives pour les CSM thérapeutiques

Le mythe de Prométhée, Rubens (1611)



Potency Assays

Maumus M et al. Medecine Sciences, 2018

Pour en savoir plus…

Greffe de Cellules Souches Hématopoïétiques et maladies auto-immunes

09 : 30 ***Pr JO Bay**, Clermont-Ferrand, Agence de Biomédecine*
09 : 45 Rapport d'Activité 2022
***Pr D. Farge**, Coordonnatrice CRMR MATHEC, St-Louis, Fai2r*

REGARD SUR DEUX ANNNEES DE PANDEMIE COVID19

10 :00 En France : quelle activité clinique ? Quels protocoles de chimiothérapie ?
***Dr L. Terriou**, Hématologie, Lille*

10 : 15 Vaccination avant et après autogreffe dans les MAI, quelles propositions ?
***Dr A. Maria**, Médecine Interne, Montpellier*

10:30 HSCT for AD in times of COVID and routine vaccination - in Germany
***Pr J. Henes,** Hematology, Allemagne*

10 50 What could we do for HSCT in AD patients during COVID outbreak: in Brasil
***Dr M C. Oliveira**, Cell Therapy Center, University of Sao Paulo, Brésil*

PRECISION MEDICINE LES ENJEUX DU BIOBANKING

11:05 Can RNA gene expression guide patient selection for AHSCT in SSc?
***Dr D. Rimar,** Rhumatology, Israël*

PAUSE CAFE 11:30– 11:45

MATHEC une plateforme de coordination pour les soins aux patients avec MAI

11 : 45 PNDS thérapie cellulaire et MAI
***Pr G. Pugnet :** pour le groupe de travail national, Médecine Interne, Toulouse*

12 :00 Neuropathies inflammatoires chroniques démyélinisantes et autogreffe de CSH : suivi de la cohorte nationale MATHEC
***Dr F. Urbain,** Médecine Interne, Hôpital Bicêtre*

12 : 15 De la RCP MATHEC au registre MATHEC-SFGM-TC
***Mme P. Lansiaux,** Coordonnatrice d'études cliniques CRMR MATHEC, St-Louis, Fai2r*

12 :30 La collecte des données pour tous et par tous: pourquoi? Comment?
***Mme I. Munia** TEC CRMR MATHEC, St-Louis, Fai2r*

12 :45 Vers un CRF MATHEC-SFGMTC standardisé ?
***Dr C. Beuvon**, Médecine Interne, Poitiers*

20 Janvier 2023

6ème journée MATHEC

2ÈME CONGRÈS FRANÇAIS DE MÉDECINE RÉGÉNÉRATRICE ET DE BIOTHÉRAPIE

Vendredi 30 septembre 2022 (8H30-17H00)
Nouvelle Faculté de Médecine - Montpellier

Thérapie cellulaire et maladies auto-immunes
14 : 00 – 16 :30

UTILISATION DES CART DANS LE TRAITEMENT DES MAI

14 : 00 Utilisation des CART cells dans le traitement du Lupus en pratique clinique ?
***Pr G. Schett**, Deutsches Zentrum für Immuntherapy, Department of Internal Medicine, Allemagne*

14: 30 ***To be confirmed***

UTILISATION DES CELLULES MESENCHYMATEUSES STROMALES (CSM) A VISEE THERAPEUTIQUE POUR LES MAI

15 :00 Immunomonitoring et potency essais en pratique clinique: de l'hétérogénéité des mécanismes d'action des CSM
***Pr K. Tarte,** Rennes, SITI EFS, INSERM UMR 1236*

15 : 30 Sclérose en Plaques : nouvelles approches cellulaire et moléculaire en immunologie
***Dr L. Michel,** Neurologie, Rennes*

15 :50 Utilisation des Cellules Mésenchymateuses Stromales dans le traitement de Sclérodermie et du Lupus : quels progrès ?
***Pr D. Farge**, Coordonnatrice CRMR MATHEC, St-Louis, Fai2r*

16 :10 Thérapie cellulaire dans les maladies auto-immunes : le rôle du pharmacien
***Dr JR. Fabreguettes,** Pharm D PhD, AGEPS (Agence Générale des équipements et produits de santé), AP-HP*

16 :30 Conclusions
***Pr D. Farge,** Coordonnatrice CRMR MATHEC, St-Louis, Fai2r*

MATHEC Maladies Auto-Immunes & Thérapie Cellulaire | Maladies Auto-immunes et Thérapie Cellulaire

https://mathec.com

U1183: Team 1 - Christian JORGENSEN

Group 3 : MSCs biology and cartilage regeneration

Danièle NOEL
Philippe GUILPAIN

Claire BONY-GARAYT
Marie MAUMUS
Pauline ROZIER
Karine TOUPET

Alexandre MARIA
Alexandre THERON
Claire LOUSSOUARN

Jérémy BOULESTREAU
Noémie PETIT JEAN
Jérémy SALVADOR
Marjorie DUFAUD