

RENCONTRES VIEILLISSEMENT

XX^{ÈME}
EDITION

RENCONTRES PLURIDISCIPLINAIRES • CITE DE LA SANTE 20 RUE DU PONT SAINT PIERRE (PROCHE LA GRAVE) TOULOUSE

8-9 NOVEMBRE 2018 • TOULOUSE

Direction
Scientifique



**La médecine régénérative : un traitement possible
pour les pathologies liées à l'avance en âge ?**

Louis Casteilla, PhD
e-mail: louis.casteilla@inserm.fr

“STROMALab” (www.stromalab.fr)
UMR ERL CNRS 5311 UPS EFS 5273, U1031 Inserm
Toulouse, FRANCE



RENCONTRES VIEILLISSEMENT

XXÈME
EDITION

RENCONTRES PLURIDISCIPLINAIRES • CITE DE LA SANTE 20 RUE DU PONT SAINT PIERRE (PROCHE LA GRAVE) TOULOUSE

8-9 NOVEMBRE 2018 • TOULOUSE

Direction
Scientifique



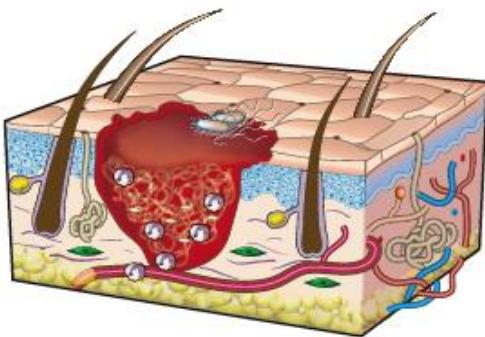
La médecine régénérative : un traitement possible pour les pathologies liées à l'avance en âge ?

- *Régénération, médecine régénératrice & vieillissement*
- *Quelles propositions thérapeutiques ?*



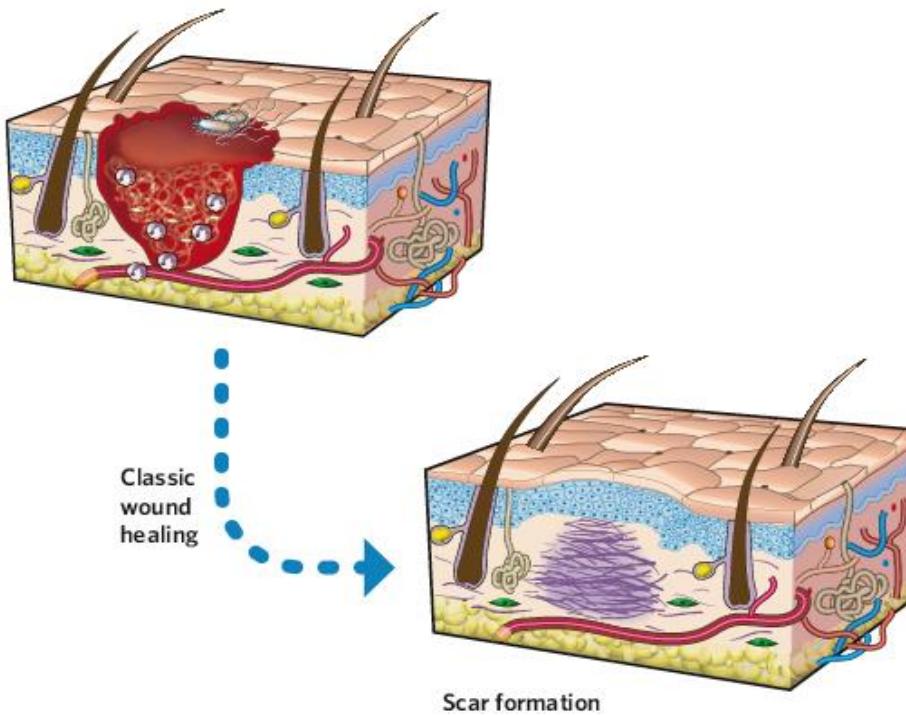
Réparation, cicatrisation et régénération

Agression
tissulaire



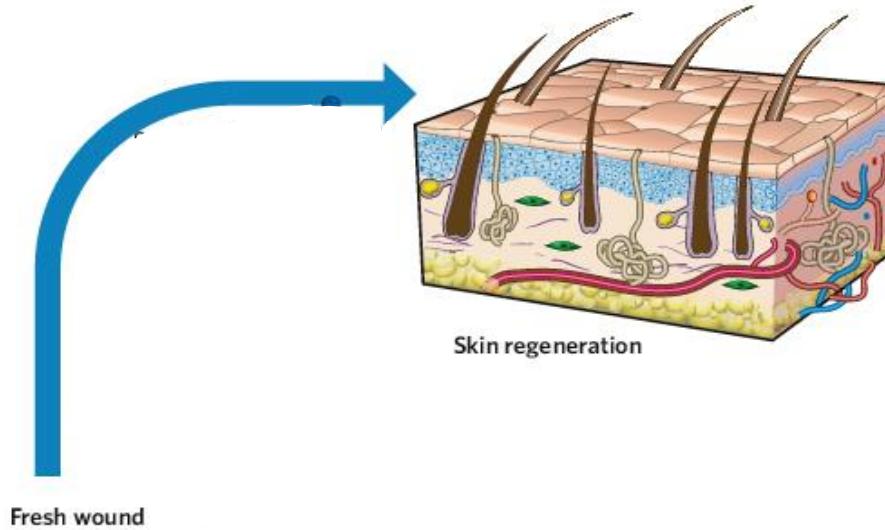
Réparation, cicatrisation et régénération

Agression
tissulaire

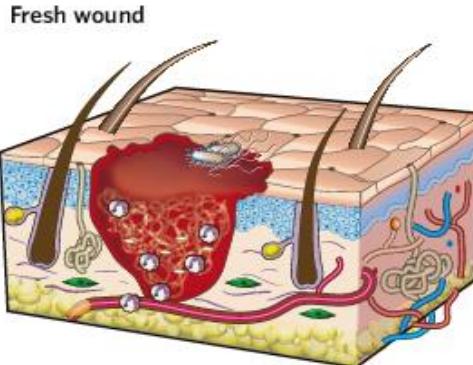


CICATRISATION:
PERTE DE
FONCTION

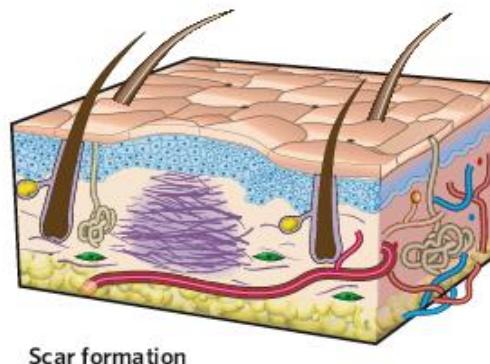
Réparation, cicatrisation et régénération



**REGENERATION:
RETABLISSEMENT
DE FORME ET DE FONCTION**



Classical
wound
healing



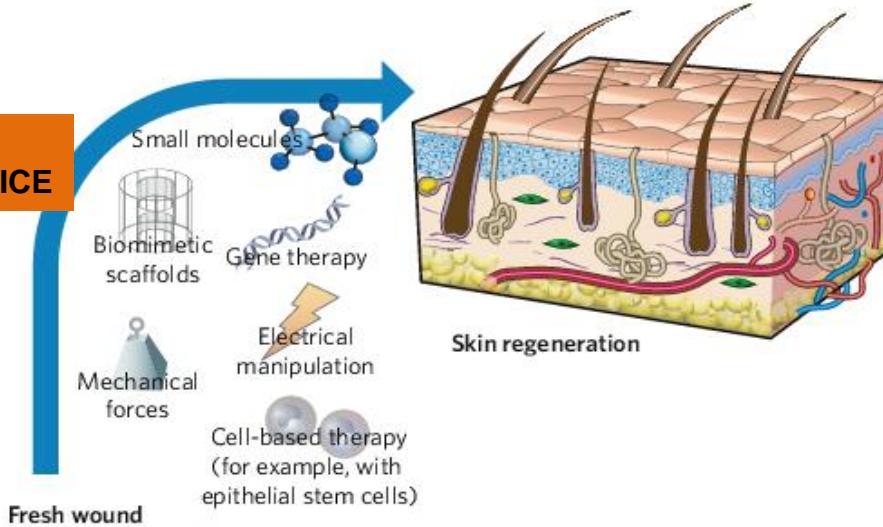
**CICATRISATION:
PERTE DE
FONCTION**

Avantage sélectif !!!

Médecine régénératrice

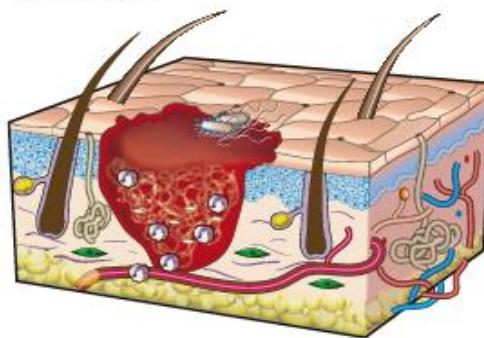
MEDECINE
REGENERATRICE

Cellule
souche

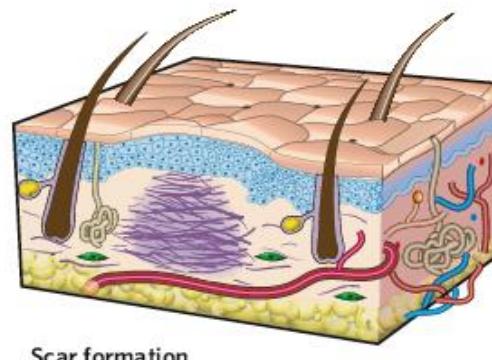


REGENERATION:
RETABLISSEMENT
DE FORME ET DE FONCTION

Aggression
tissulaire



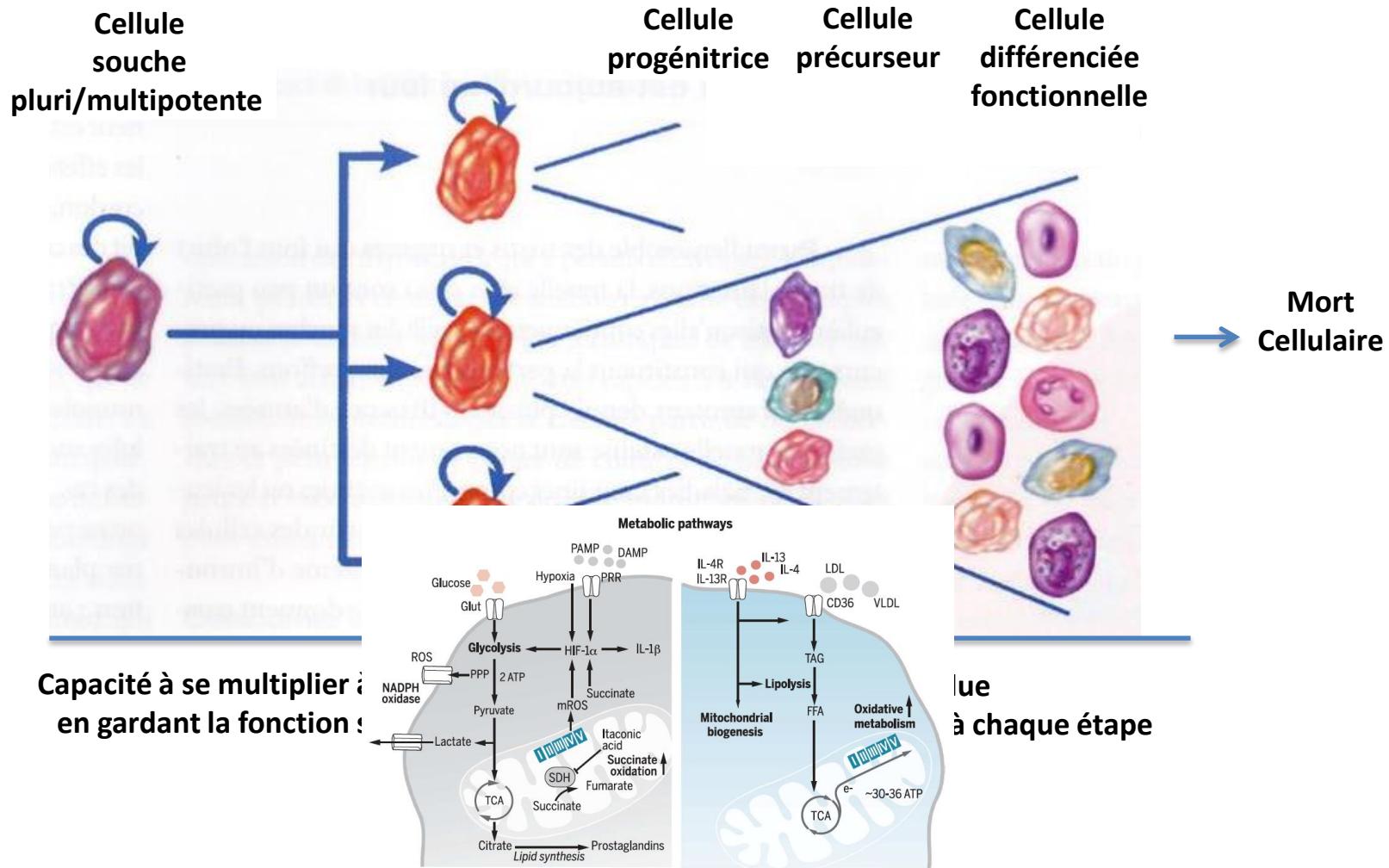
Classic
wound
healing



CICATRISATION:
PERTE DE
FONCTION

Médecine régénératrice

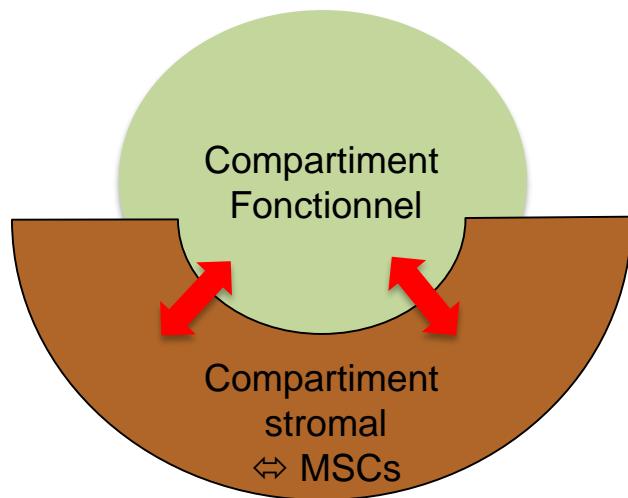
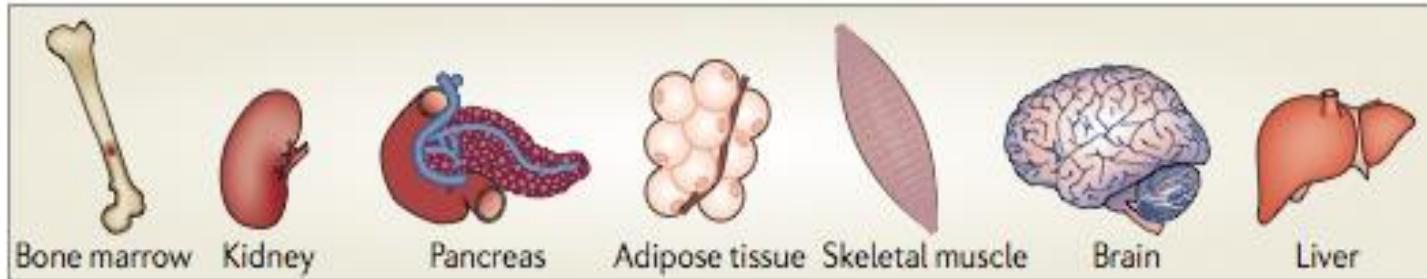
Rationnel 1 : un turn-over permanent



Un acteur obligatoire: le métabolisme

Médecine régénératrice

Rationnel 2: Fonction = Parenchyme + Mésenchyme



Parenchyme
(spécifique
30-40% cell)

Neurones
Cardiomyocytes
Cellules musculaires
Hépatocytes
...

↔ Cell. souches
spe

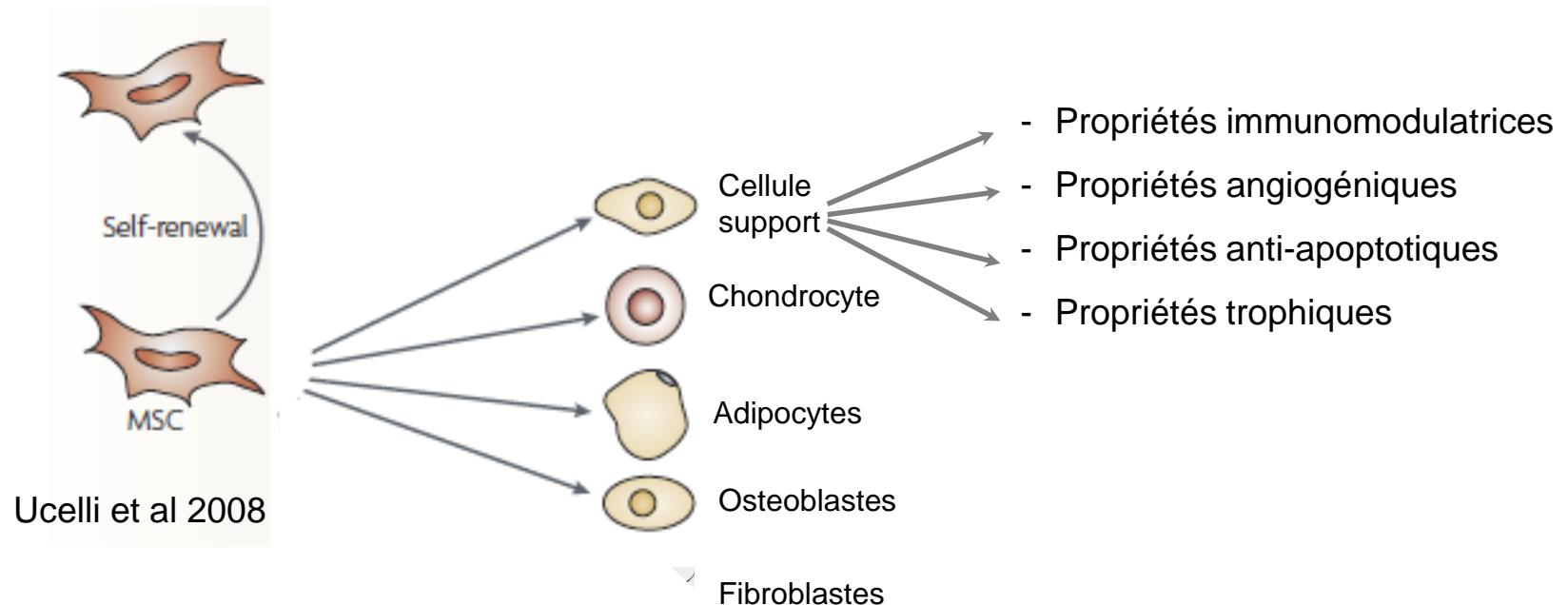
Mésenchyme
(transversal)

↔ Cell.
souches/stromales
mésenchymateuses

Médecine régénératrice

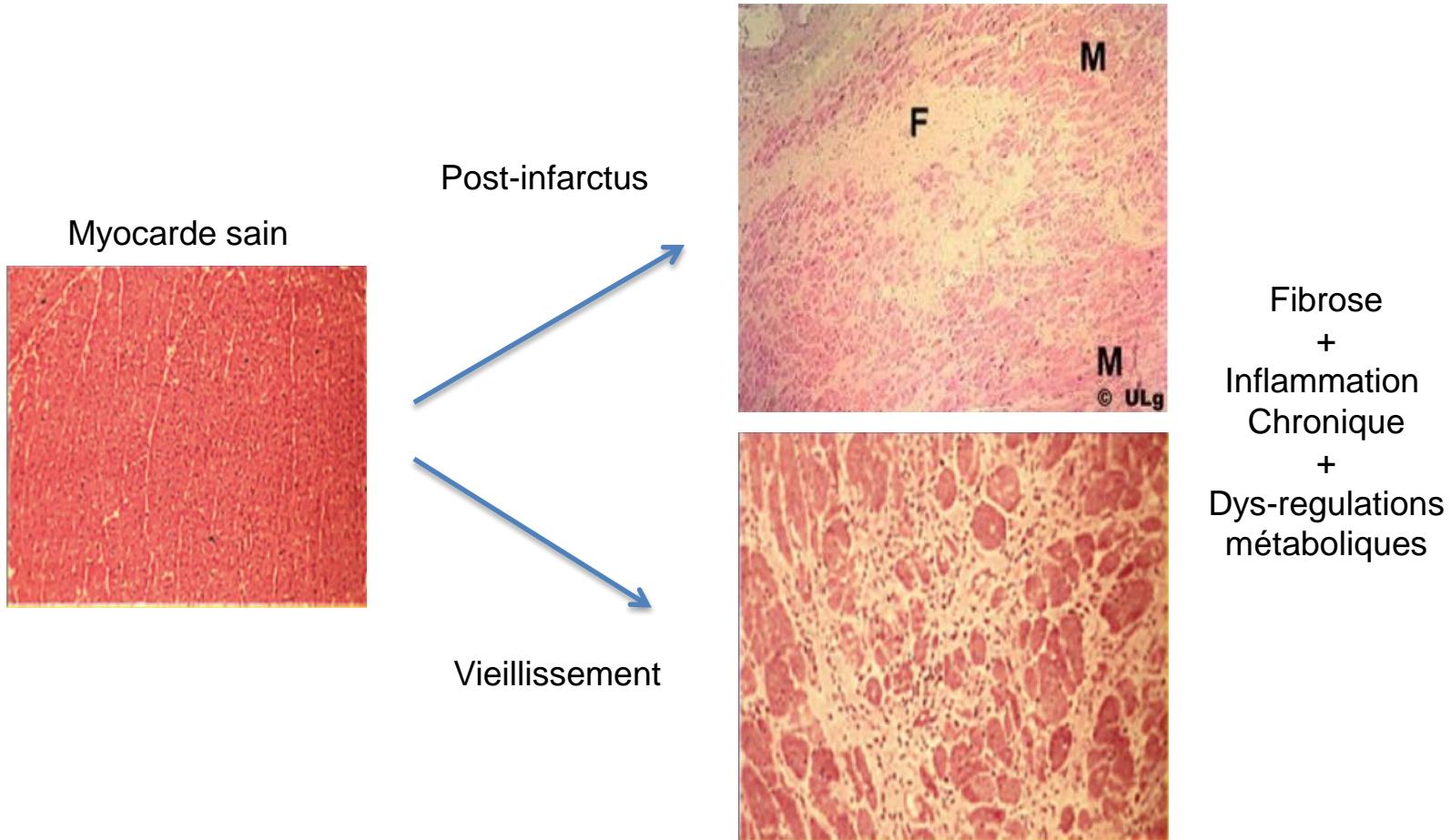
Rationnel 2: Fonction = Parenchyme + Mésenchyme

Les Cellules Souches Mésenchymateuses (MSC)



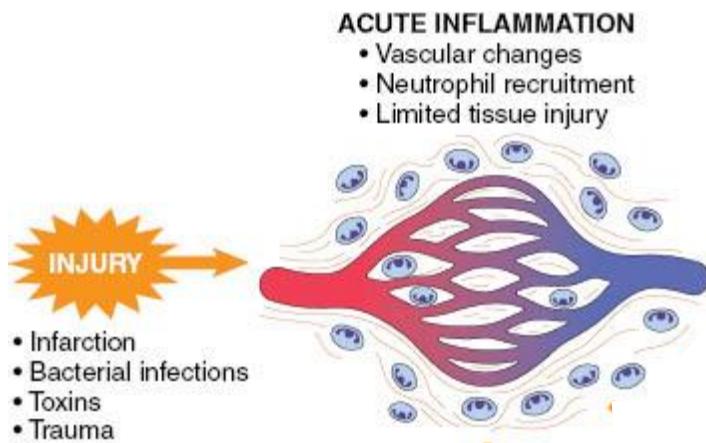
Médecine régénératrice

Rationnel 3 : Le vieillissement comme une cicatrisation évolutive à l'échelle de l'organisme



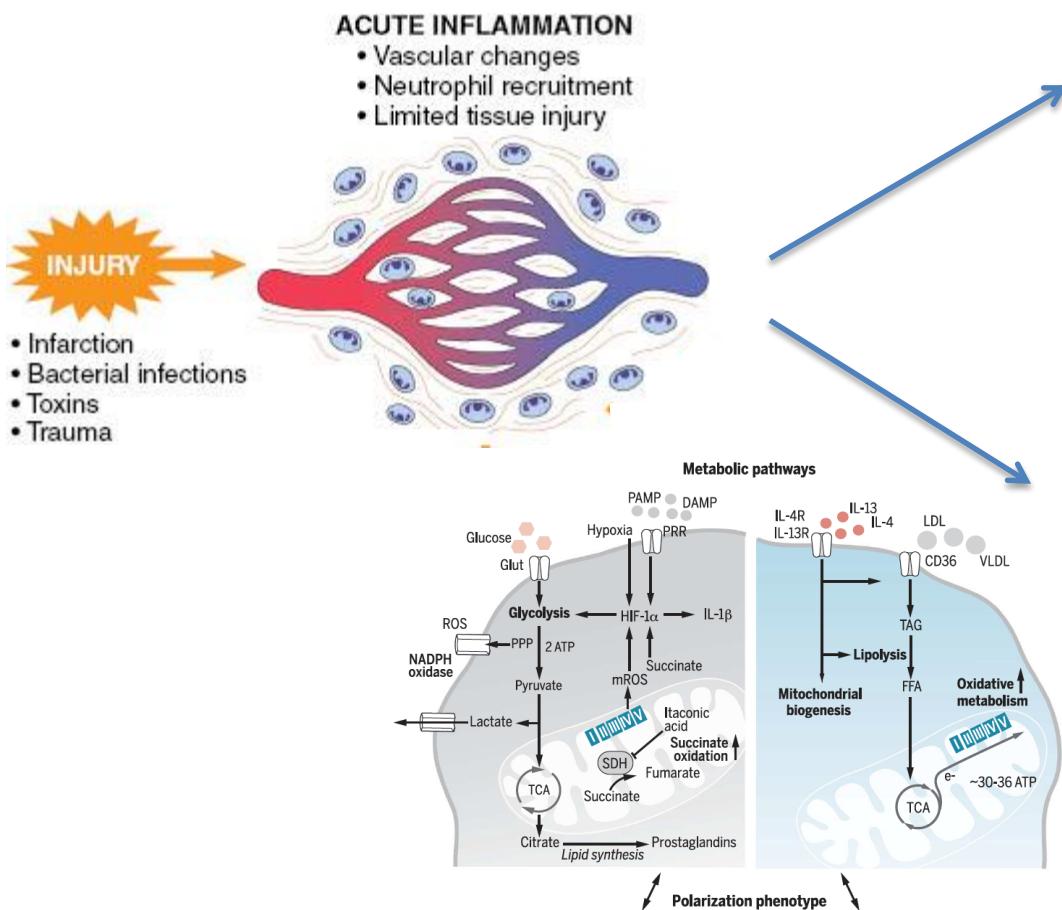
Médecine régénératrice

Rationnel 3 : Le vieillissement comme une cicatrisation évolutive à l'échelle de l'organisme



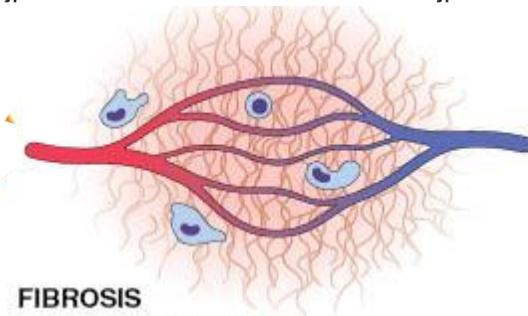
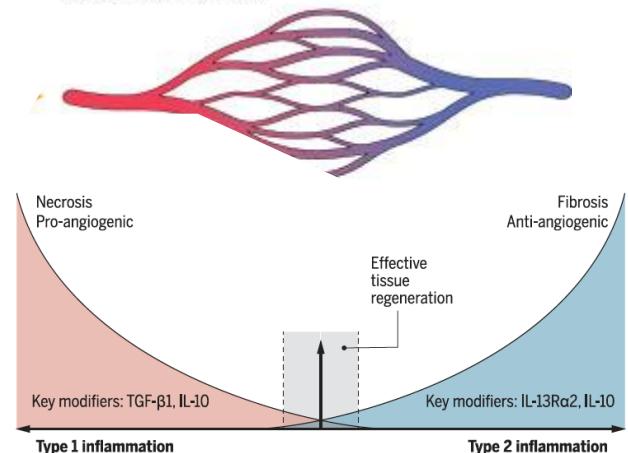
Médecine régénératrice

Rationnel 3 : Le vieillissement comme une cicatrisation évolutive à l'échelle de l'organisme



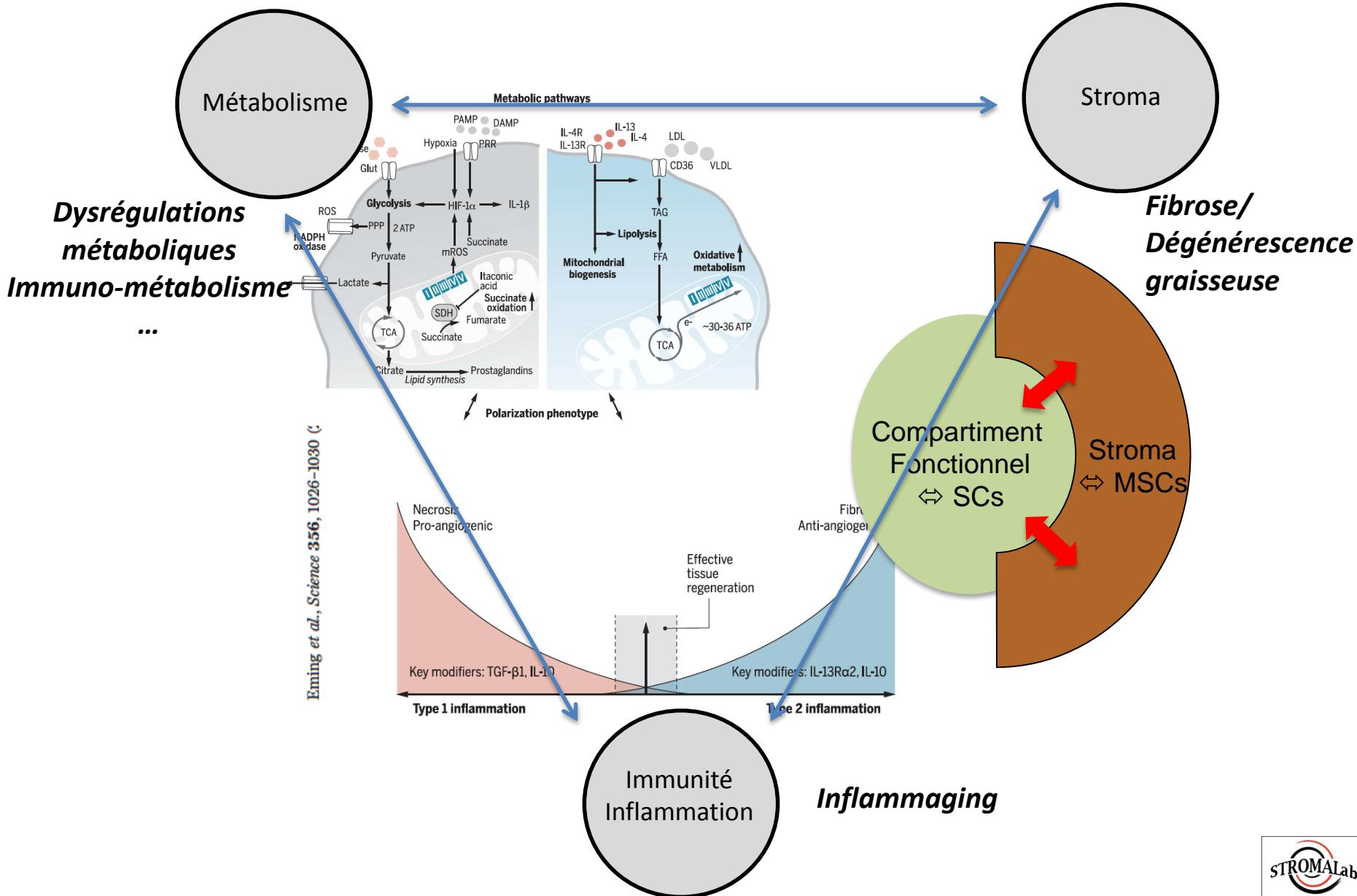
RESOLUTION

- Clearance of injurious stimuli
- Clearance of mediators and acute inflammatory cells
- Replacement of injured cells
- Normal function



Médecine régénératrice

Rationnel : les éléments clés

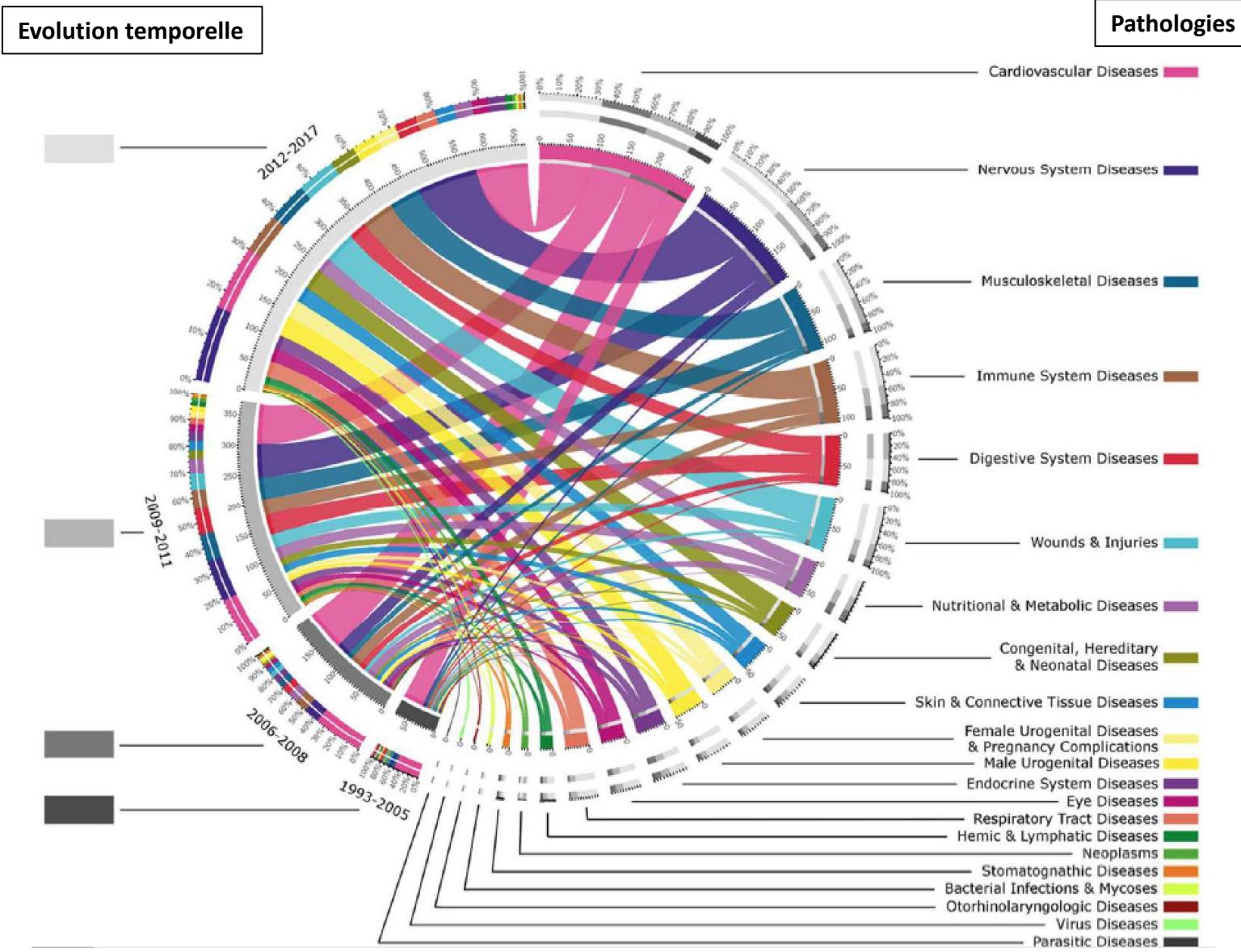


La médecine régénératrice

- *Quelles propositions thérapeutiques ?*

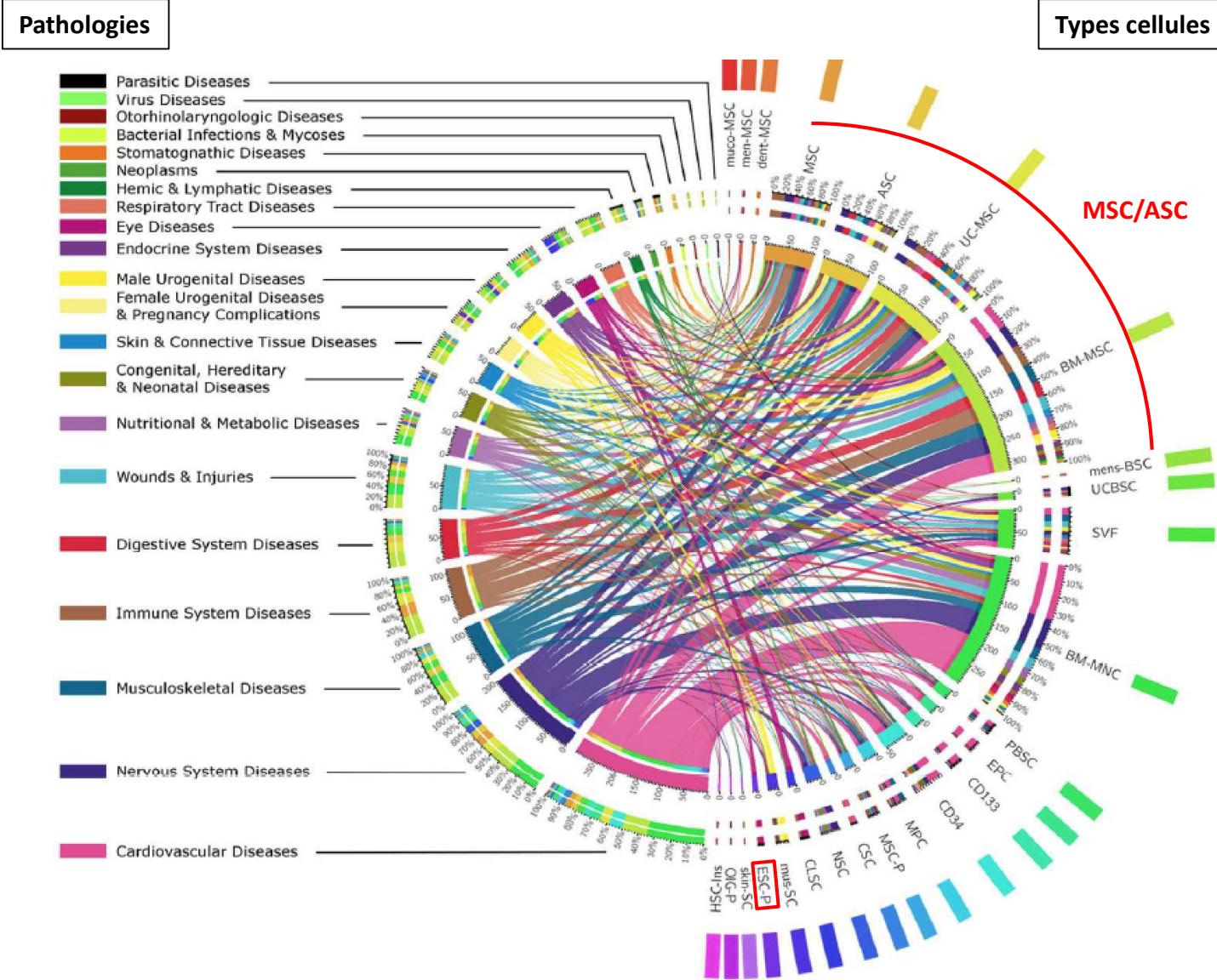


Médecine régénératrice: essais cliniques

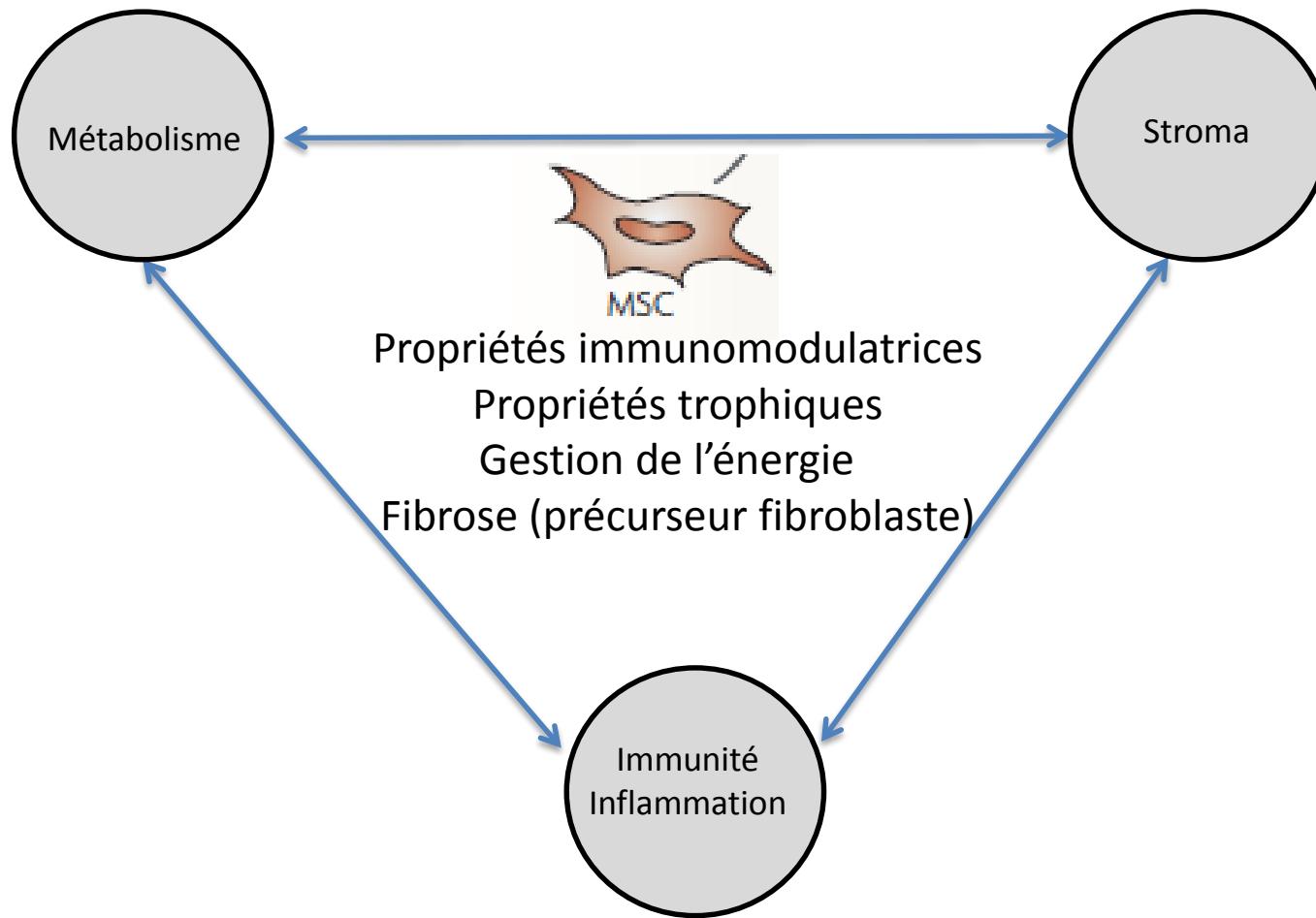


Montsarrat et al, Stem Cell Transl Med, 2016

Médecine régénératrice: essais cliniques



Médecine régénératrice: essais cliniques



Médecine régénératrice: essais cliniques

AMM: ASC & Inflammation/Immunity: Crohn disease

Adipose-Derived Mesenchymal Stem Cells Alleviate Experimental Colitis by Inhibiting Inflammatory and Autoimmune Responses

MANUEL A. GONZÁLEZ,^{*,‡} ELENA GONZALEZ-REY,[§] LAURA RICO,^{*} DIRK BÜSCHER,^{*} and MARIO DELGADO[§]

*Cellerix SA, Tres Cantos (Madrid), Madrid; [‡]Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid; and [§]Instituto de Parasitología y Biomedicina-CSIC, Granada, Spain

GASTROENTEROLOGY 2009;136:978–989

Long-term follow-up of patients undergoing adipose-derived adult stem cell administration to treat complex perianal fistulas

Hector Guadalajara · Dolores Herreros ·
Paloma De-La-Quintana · Jacobo Trebol ·
Mariano Garcia-Arranz · Damian Garcia-Olmo

Int J Colorectal Dis (2012) 27:595–600

Autologous Adipose Tissue-derived Stem Cells Treatment Demonstrated Favorable and Sustainable Therapeutic Effect for Crohn's Fistula

Woo Yong Lee, MD, PhD,¹ Kyu Joo Park, MD, PhD,² Yong Beom Cho,¹ Yoon, MD, PhD,³ Kee Ho Song, MD,⁴ Do Sun Kim, MD,⁴ Sang Hun Jung, MD, PhD,⁵ Mihyung Kim, PhD,⁶ Hee-Won Yoo, PhD,⁶, Inok Kim, MS,^{6,7} Hyunjoo Ha, PhD,⁷ Chang Sik Yu, MD, PhD³

Médecine régénératrice: essais cliniques

L'expérience toulousaine

Médecine régénératrice: essais cliniques

L'expérience toulousaine



Filière Médecine régénératrice « Langlade »

Recherche



Essais cliniques

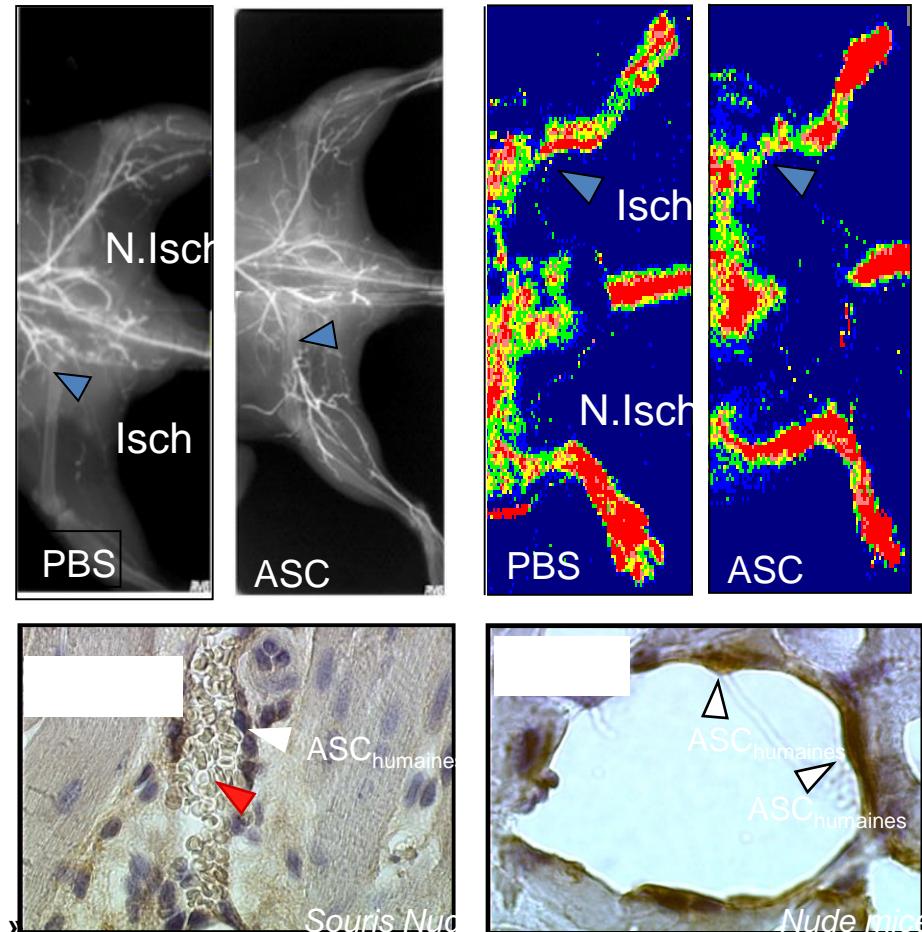
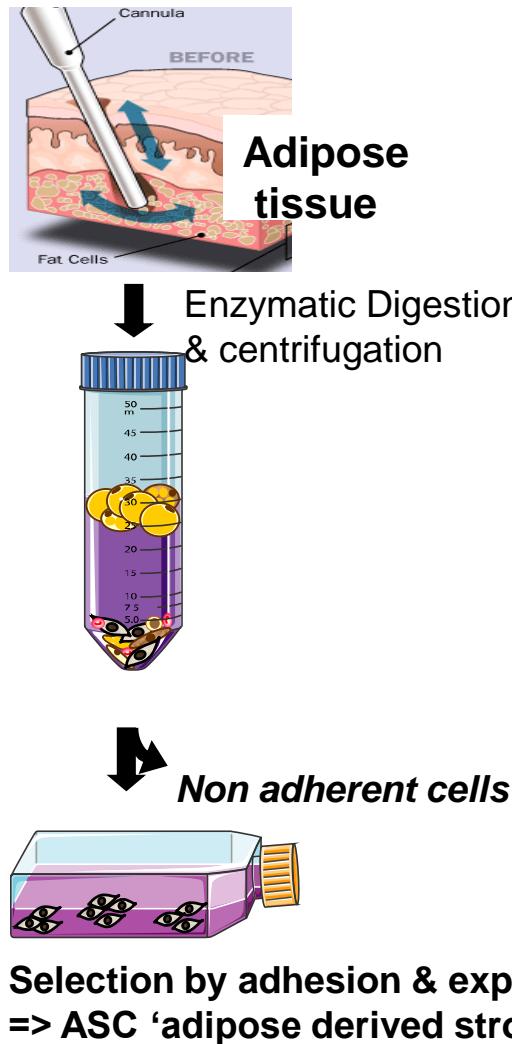


- Recherche amont (Univ, Inserm, CNRS, Ecole Ing,)
- Plate-forme nationale Contrôle qualité in vitro (sécurité, efficacité)
- Plate-forme sécurité, biodistribution PBL (ENVT)
- Etablissement pharmaceutique de production
- CHU



Médecine régénératrice: essais cliniques

L'expérience toulousaine



Médecine régénératrice: essais cliniques

L'expérience toulousaine

Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia Bura et al *Cyotherapy*, 2014; 16: 245–257

Promotor: CHU Rangueil

Coordination : Clinic Investigating Center –Biotherapy

PI: Pr Bura-Rivièred

Cell process and quality controls: EFS/STROMA lab

2 weeks

6 months

Sampling
(30g)

Cell expansion (P1)
(GMP conditions)

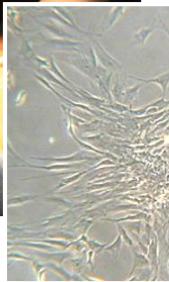
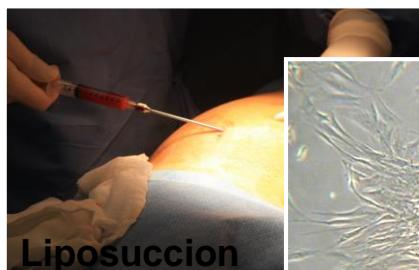
Injection
i.m.
(10^8 ASCs)

Follow up

Last visit

Feasible

No adverse
events



Médecine régénératrice: essais cliniques

L'expérience toulousaine

Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia Bura et al *Cyotherapy*, 2014; 16: 245–257

Table IV. Main results for all enrolled patients after the day of ASC transplantation (EVA).

| Case | Rutherford grade | | Rest pain (EVA) | | TcPO ₂ (mm Hg) | | ABI | | No. of ulcers | | | Amputation |
|------|------------------|---------|-----------------|---------|---------------------------|----------------------------|-------|---------|---------------|-----------|--|----------------|
| | Day 0 | Day 180 | Day 0 | Day 180 | Day 0 | Changes (end point, day 0) | Day 0 | Day 180 | Day 0 | End point | | |
| 1 | III-6 | II | 6 | 0 | 26 | +8 | 0.46 | 0.36 | 3 | 0 | | None |
| 2 | III-6 | NA | 6 | NA | 0 | NA | 0.3 | NA | 2 | NA | | Major, day 30 |
| 3 | III-6 | III-5 | 8 | 3 | 15 | +9 | 0.65 | 0.56 | 4 | 2 | | None |
| 4 | III-6 | NA | 4 | NA | 8 | -5 | 0.46 | NA | 6 | 4 | | Major, day 150 |
| 5 | III-6 | III-5 | 7 | 4 | 4 | +24 | 0.61 | 0.81 | 1 | 1 | | None |
| 6 | III-6 | III-5 | 0 | 0 | 30 | +10 | 0.31 | 0.25 | 2 | 1 | | None |
| 7 | III-6 | NA | 7 | NA | 5 | +12 | 0.37 | 0.18 | 1 | 0 | | Major, day 90 |

Values are indicated at day 0 (day of ASC transplantation) and end point corresponding either to the day of amputation or 180 d after ASC transplantation. Rest pain and TcPO₂ were assessed by analogic scale and laser Doppler analysis, respectively.

Slight increase of TcPO₂
Modulation of inflammation
Improvement in wound healing

Médecine régénératrice: essais cliniques

L'expérience Occitane

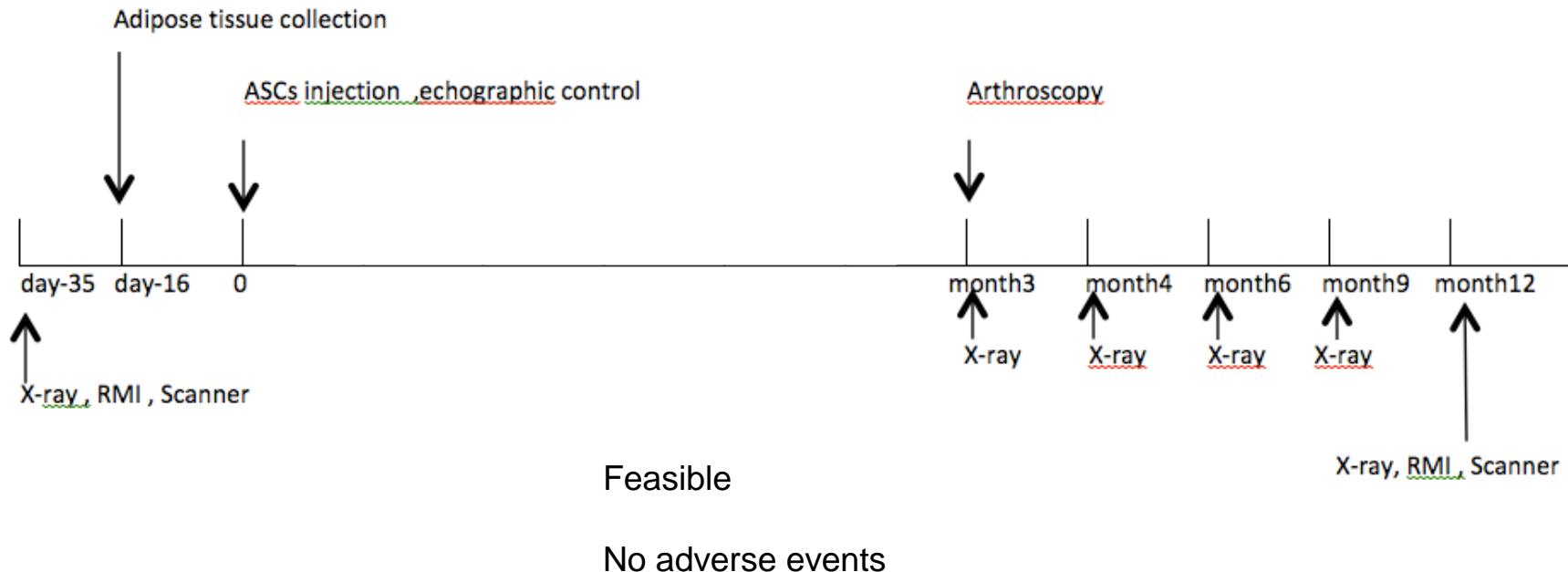


ADIPOA: Treatment of OA using autologous ASC

PIs: Pr C Jorgensen (Montpellier, France)

Pr U. Nöth (Wurzburg, Germany)

Cell process and quality controls: EFS/STROMALab



Médecine régénératrice: essais cliniques

L'expérience Occitane



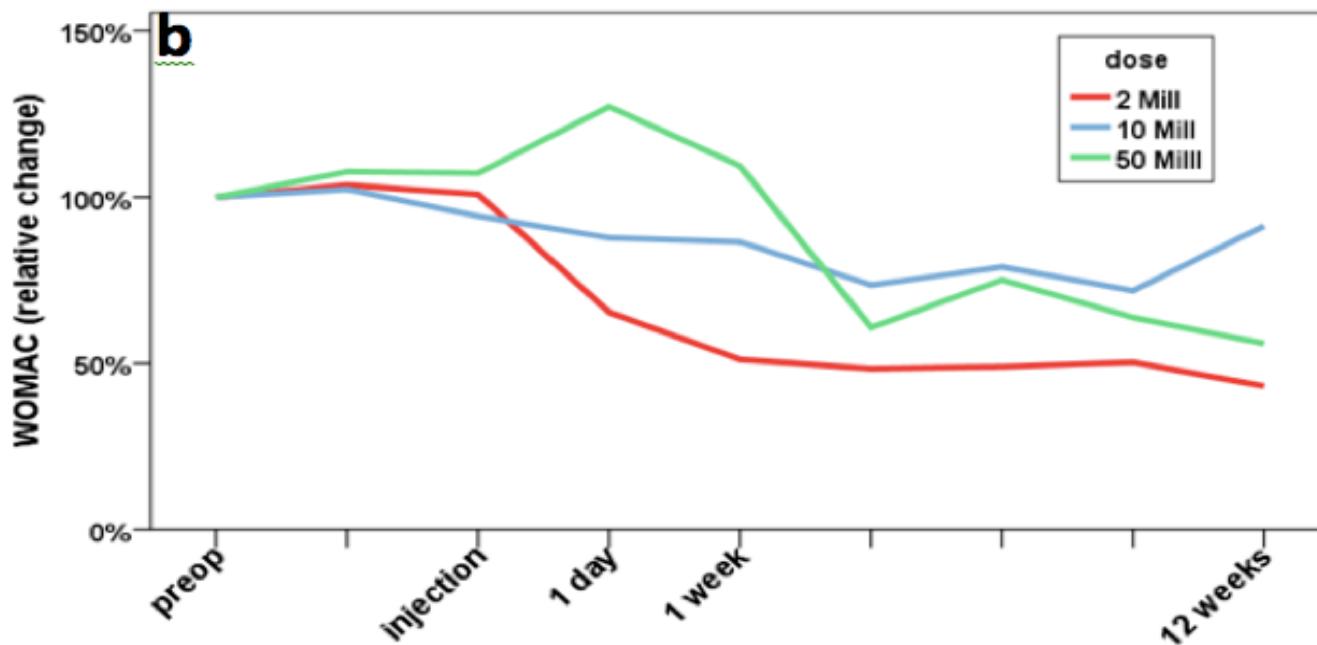
ADIPOA: Treatment of OA using autologous ASC

PIs: Pr C Jorgensen (Montpellier, France)

Pr U. Nöth (Wurzburg, Germany)

Cell process and quality controls: EFS/STROMALab

WOMAC index: level of disability by assessing pain, joint stiffness, physical as well as social and emotional function.

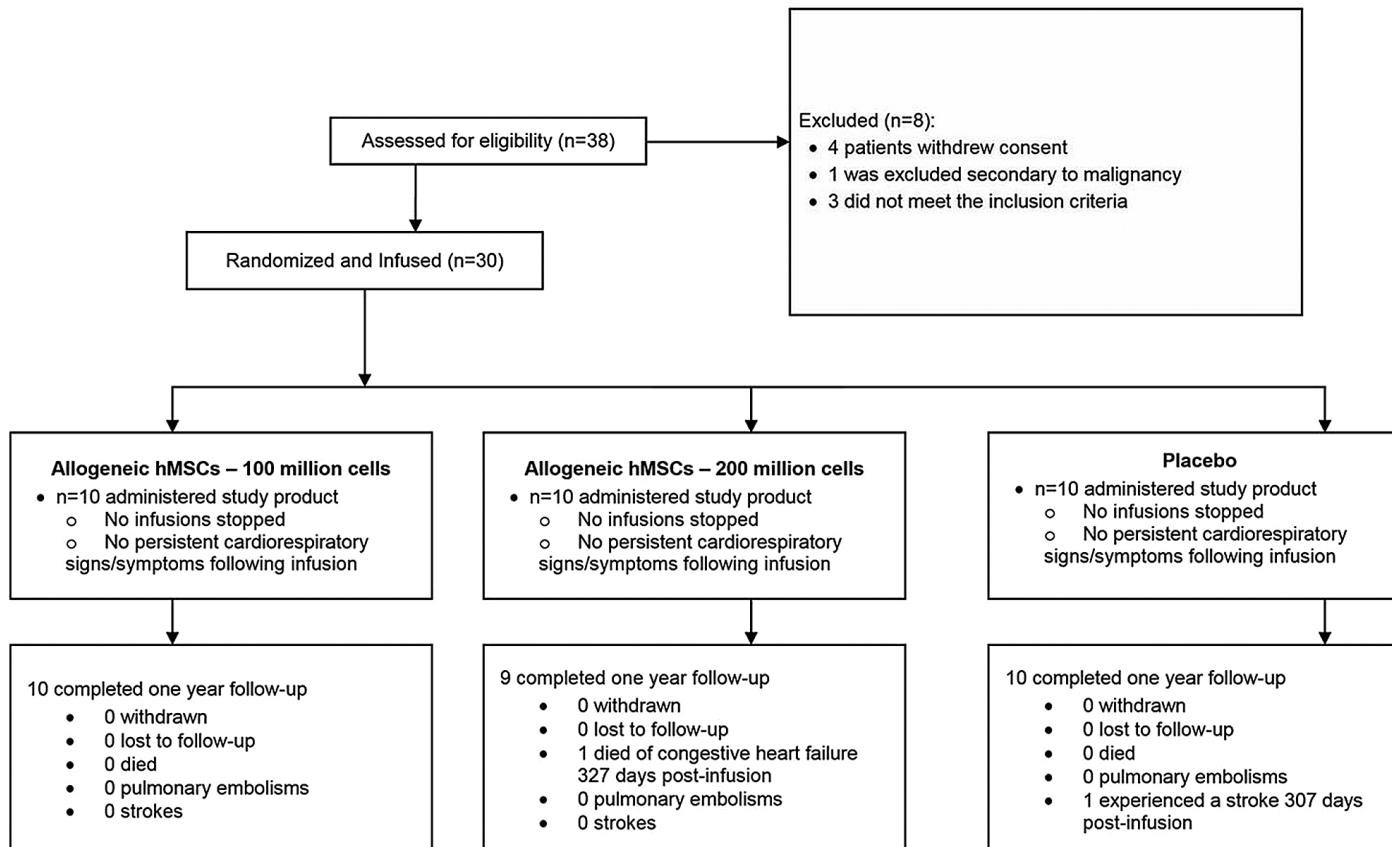


Médecine régénératrice: essais cliniques

MSC et fragilité

Allogeneic Mesenchymal Stem Cells Ameliorate Aging Frailty: A Phase II Randomized, Double-Blind, Placebo-Controlled Clinical Trial

J Gerontol A Biol Sci Med Sci, 2017, Vol. 72, No. 11, 1513–1521

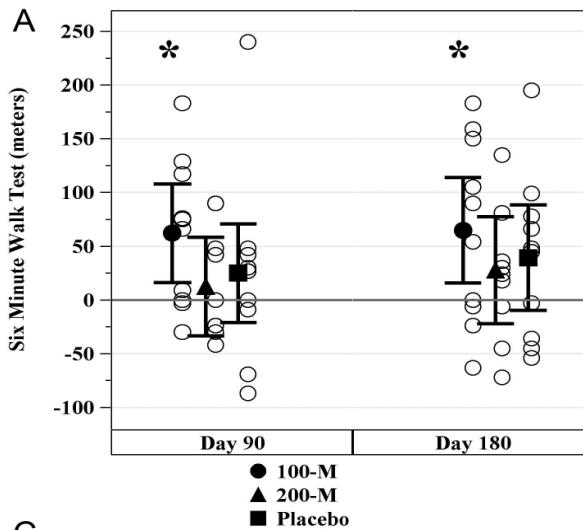


Médecine régénératrice: essais cliniques

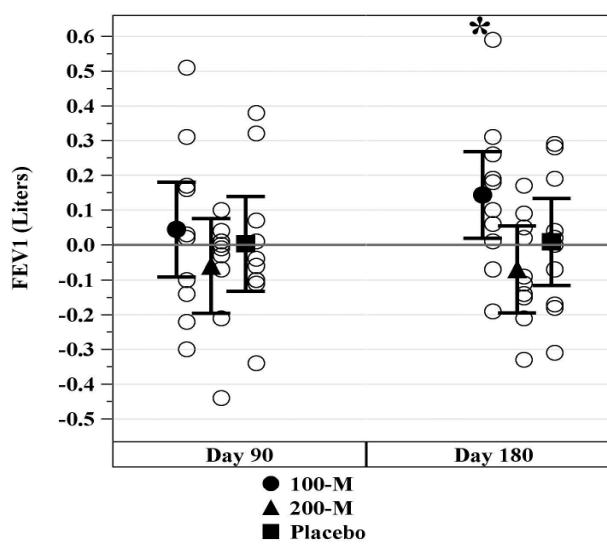
MSC et fragilité

Allogeneic Mesenchymal Stem Cells Ameliorate Aging Frailty: A Phase II Randomized, Double-Blind, Placebo-Controlled Clinical Trial

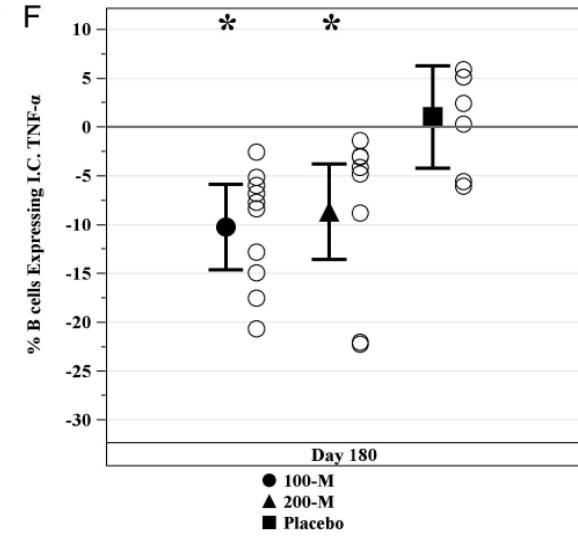
J Gerontol A Biol Sci Med Sci, 2017, Vol. 72, No. 11, 1513–1521



Distance de marche



Capacités respiratoires



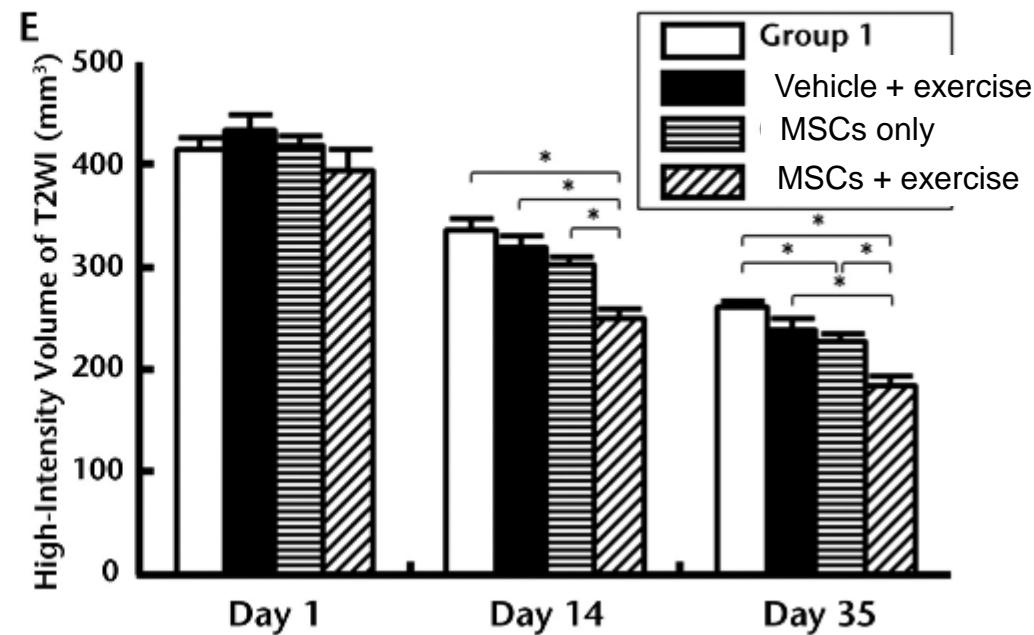
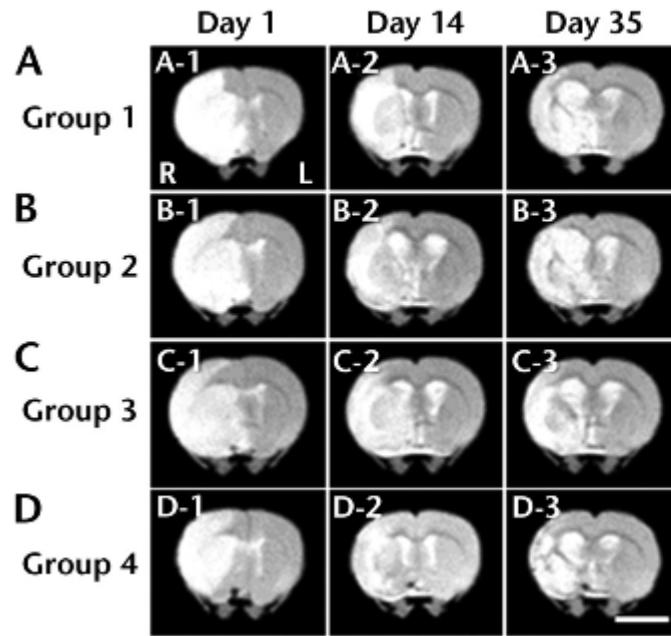
Index inflammatoires

Médecine régénératrice: le futur

Synergic Effects of Rehabilitation and Intravenous Infusion of Mesenchymal Stem Cells After Stroke in Rats

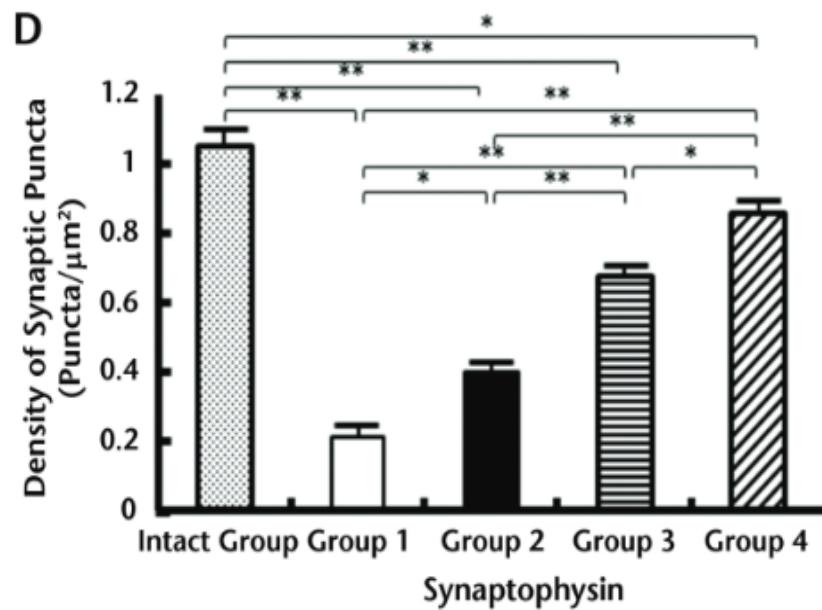
Yuichi Sasaki, Masanori Sasaki, Yuko Kataoka-Sasaki, Masahito Nakazaki,
2016 Volume 96 Number 11 Physical Therapy

Intravenous Infusion of Mesenchymal Stem Cells After Stroke



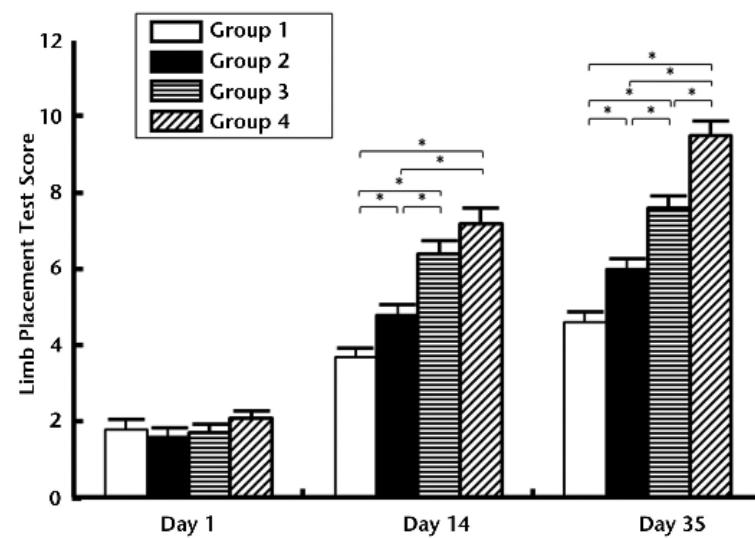
Médecine régénératrice: le futur

Synaptogenèse



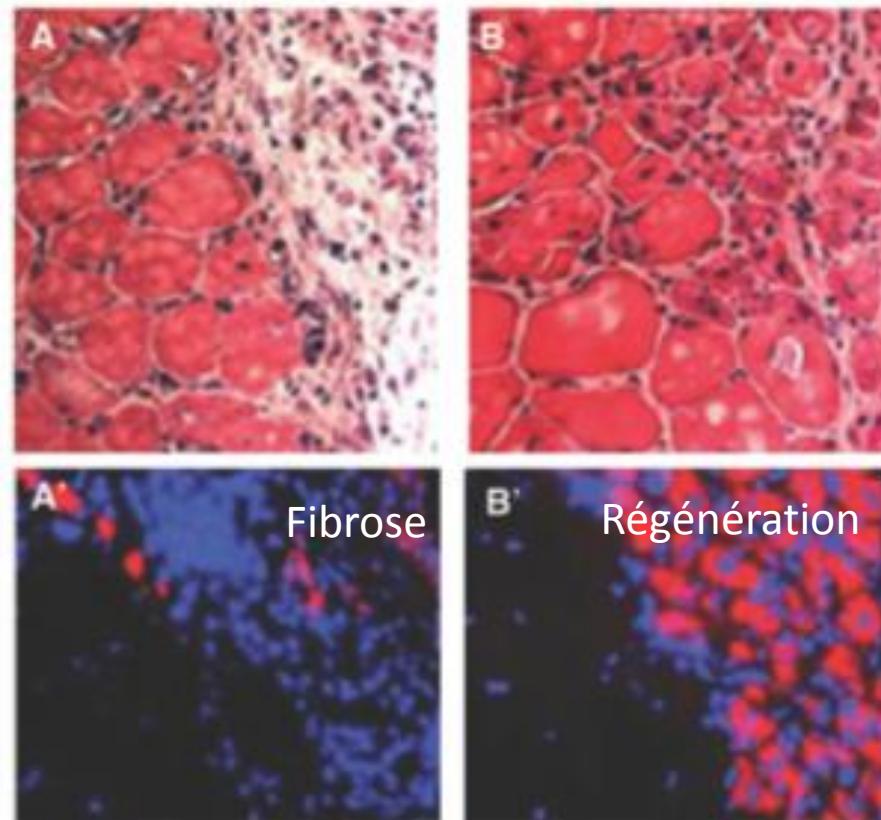
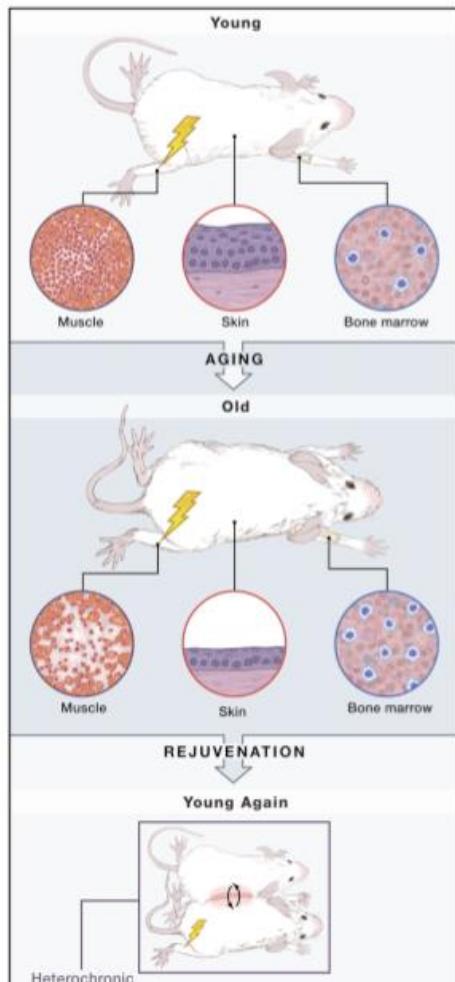
Synaptogenesis in the motor cortex in the infarcted hemisphere at layer III/IV was analyzed with a confocal microscopy.

Exercice



Médecine régénératrice: le futur

Des molécules circulantes



IA in Conroy *et al.* (2005).

Médecine régénératrice: le futur

Des molécules circulantes

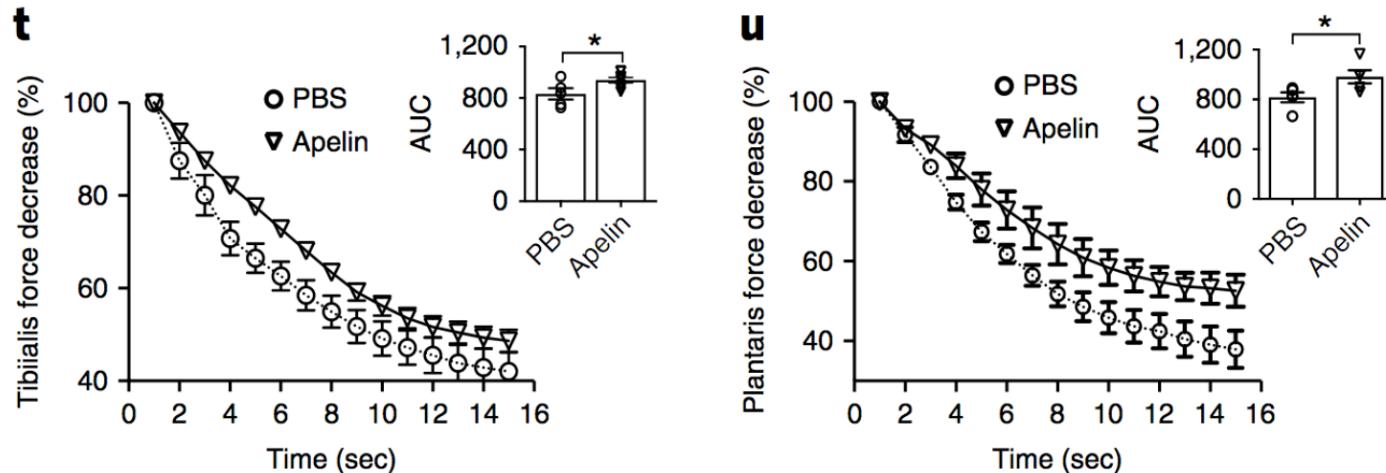
ARTICLES

<https://doi.org/10.1038/s41591-018-0131-6>

nature
medicine

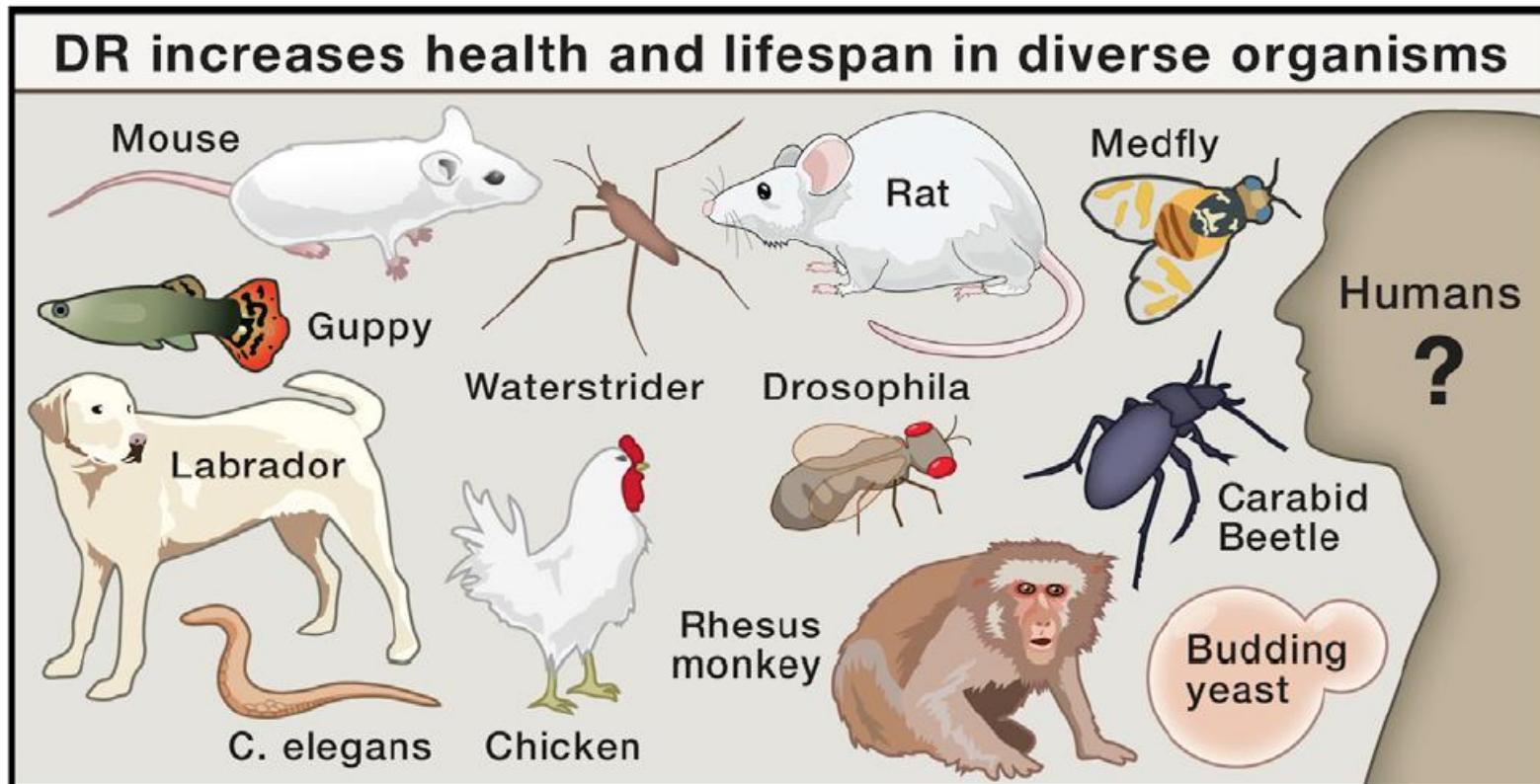
The exerkine apelin reverses age-associated sarcopenia

Claire Vinel¹, Laura Lukjanenko², Aurelie Batut¹, Simon Deleruyelle¹, Jean-Philippe Pradère¹, Sophie Le Gonidec¹, Alizée Dortignac¹, Nancy Geoffre¹, Ophelie Pereira¹, Sonia Karaz², Umji Lee², Mylène Camus³, Karima Chaoui³, Etienne Mouisel¹, Anne Bigot⁴, Vincent Mouly⁴, Mathieu Vigneau⁵, Allan F. Pagano⁶, Angèle Chopard⁶, Fabien Pillard¹, Sophie Guyonnet⁷, Matteo Cesari⁷, Odile Burlet-Schiltz³, Marco Pahor⁸, Jerome N. Feige², Bruno Vellas⁷, Philippe Valet^{1,9} and Cedric Dray^{1,9*}



Médecine régénératrice: le futur

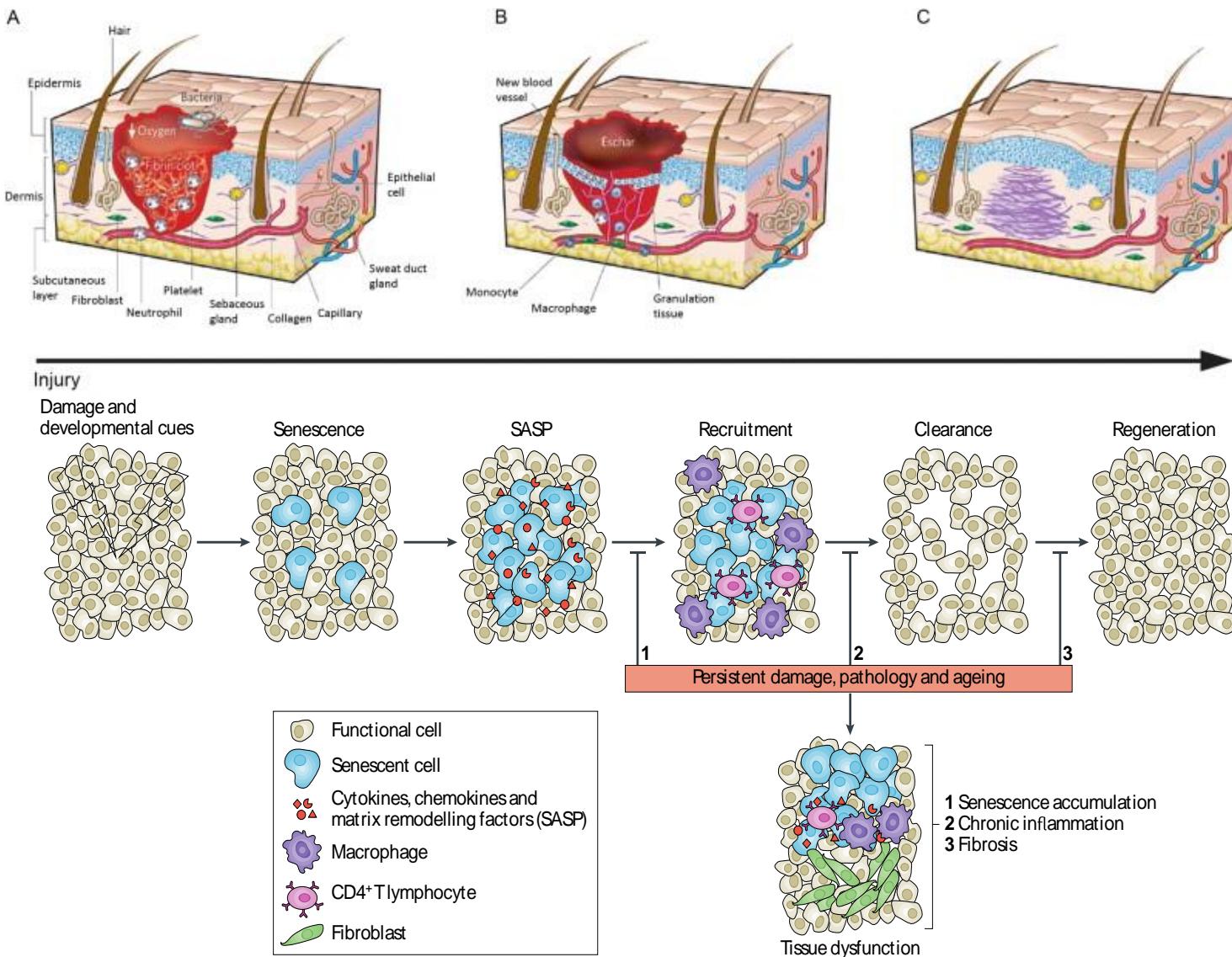
La restriction calorique



Efficace chez personnes âgées ?
Comment l'appliquer chez l'homme ?

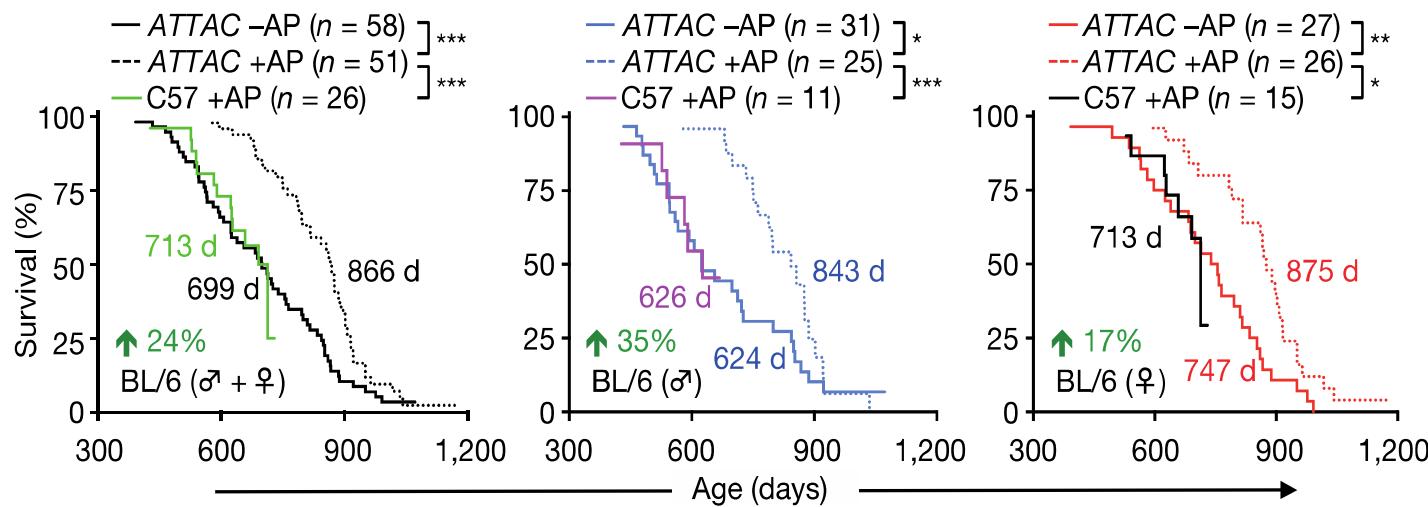
Médecine régénératrice: le futur

L'approche sénolytique

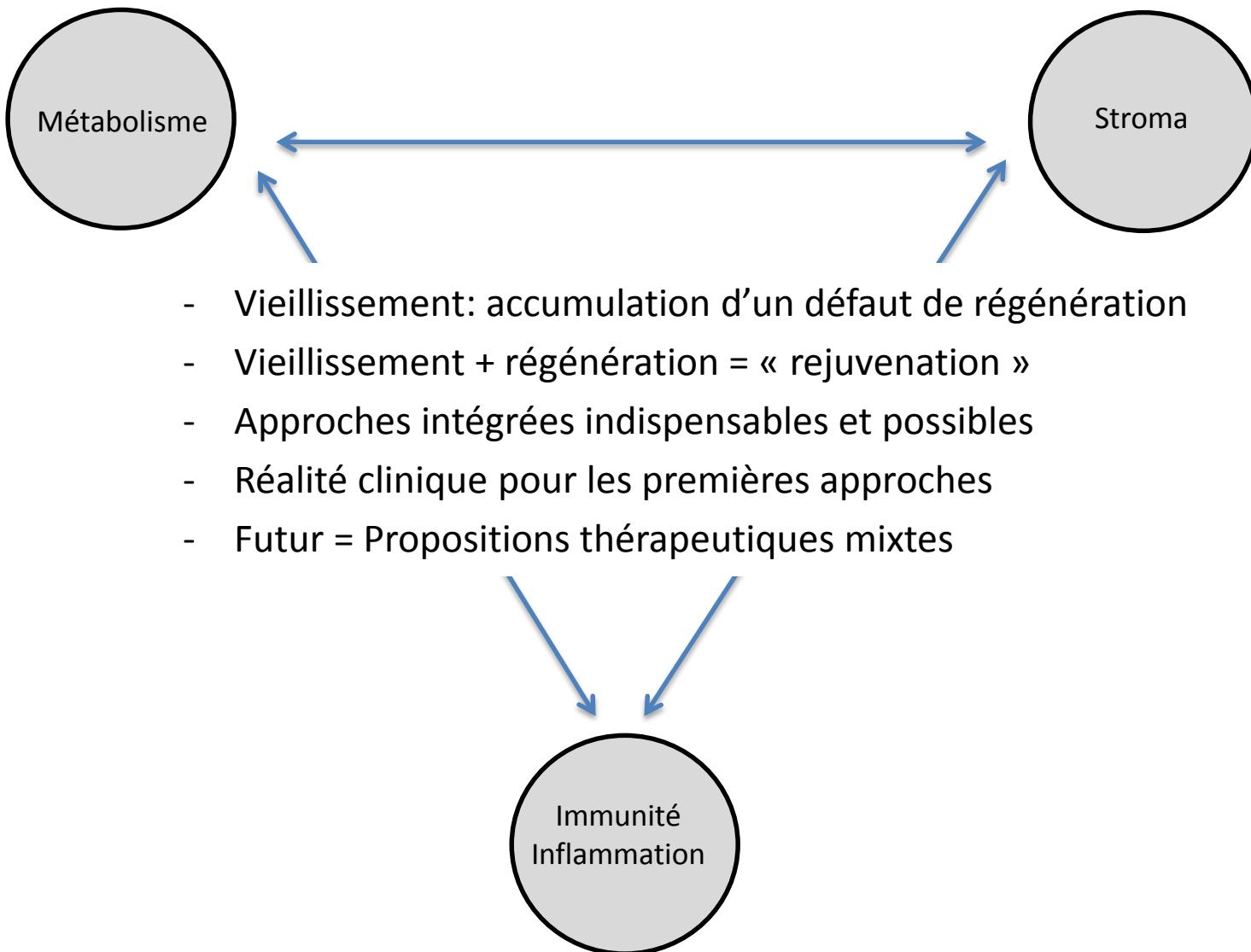


Médecine régénératrice: le futur

L'approche sénolytique



Conclusions



INSPIRE Team

B Vellas

S Andrieu

P Baretto

Y Rolland

J Delrieu

S Guyonnet

R Liblau

N Fazilleau

A Parini

C Dray

P Gourdy

P Valet

L Penicaud

I Ader

STROMALab

CIC-BT CHU Toulouse

Service Physiologie vasculaire

C Jorgensen (inserm, Montpellier)

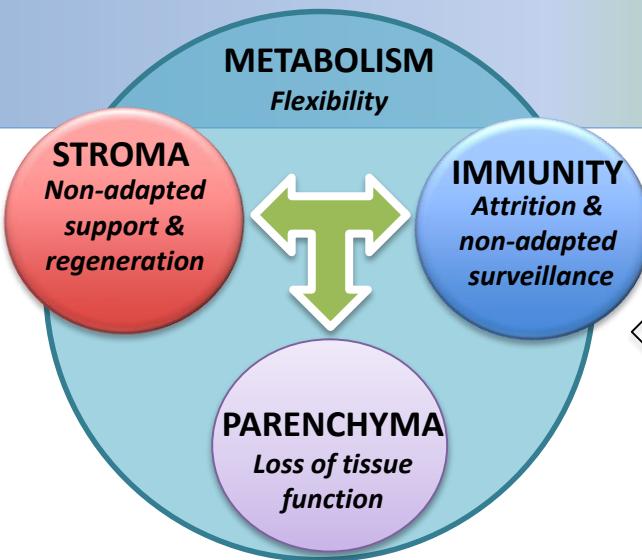




Filière INSPIRE « Healthy aging & rejuvenation »

Recherche

Recherche amont
(Univ, Inserm,
CNRS, Ecole Ing,)
(400/500 personnes
pluridisciplinaires)



Essais cliniques



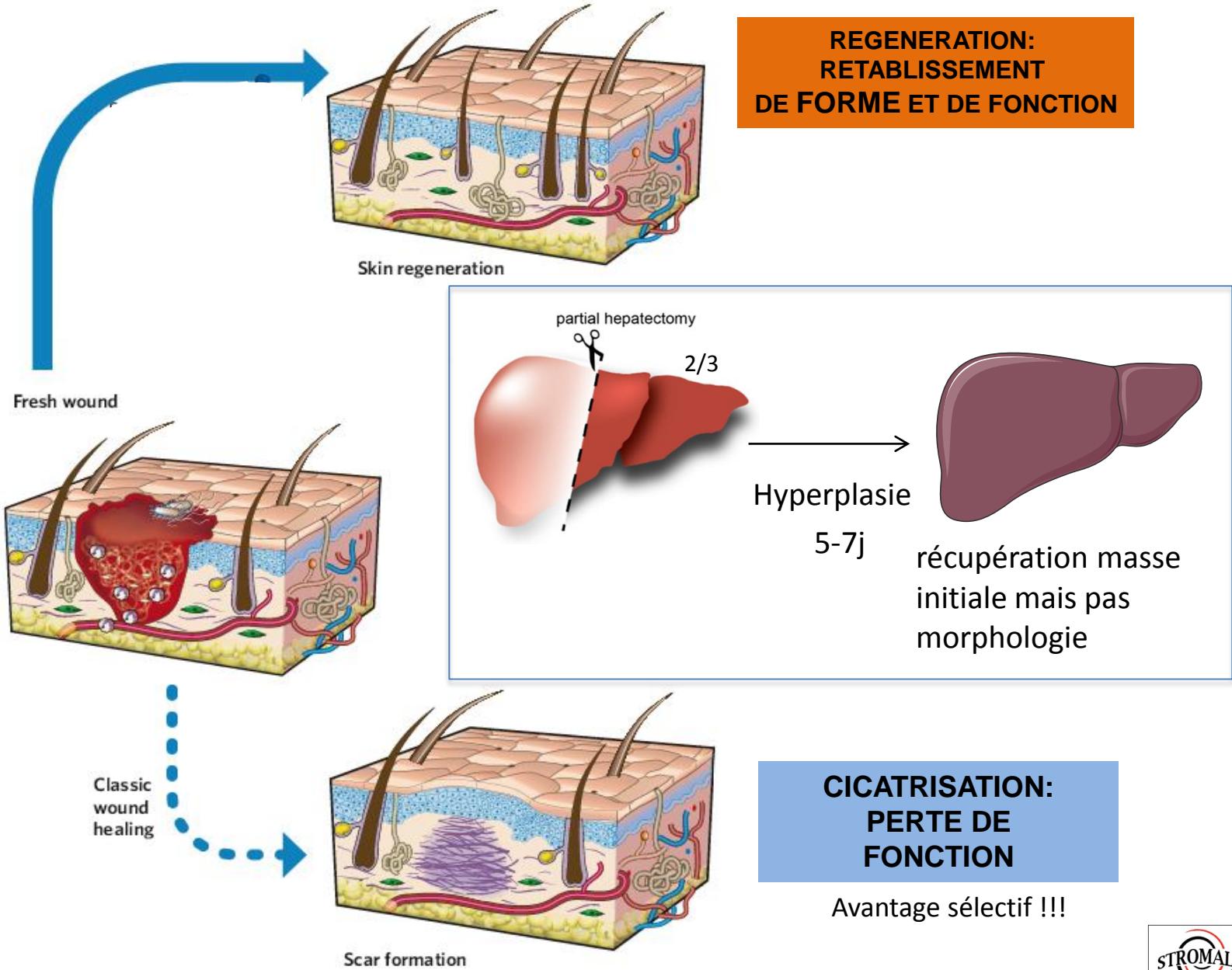
Gerontopôle,
Centre référent
OMS



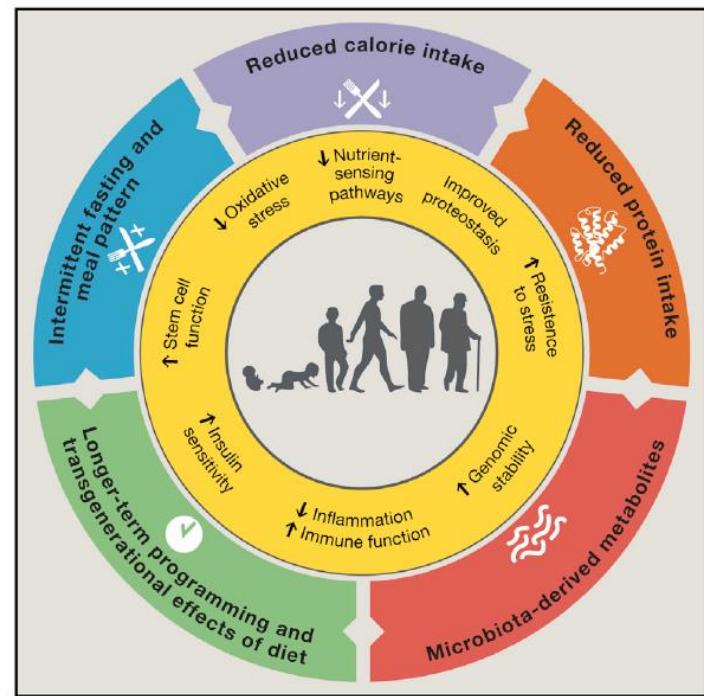
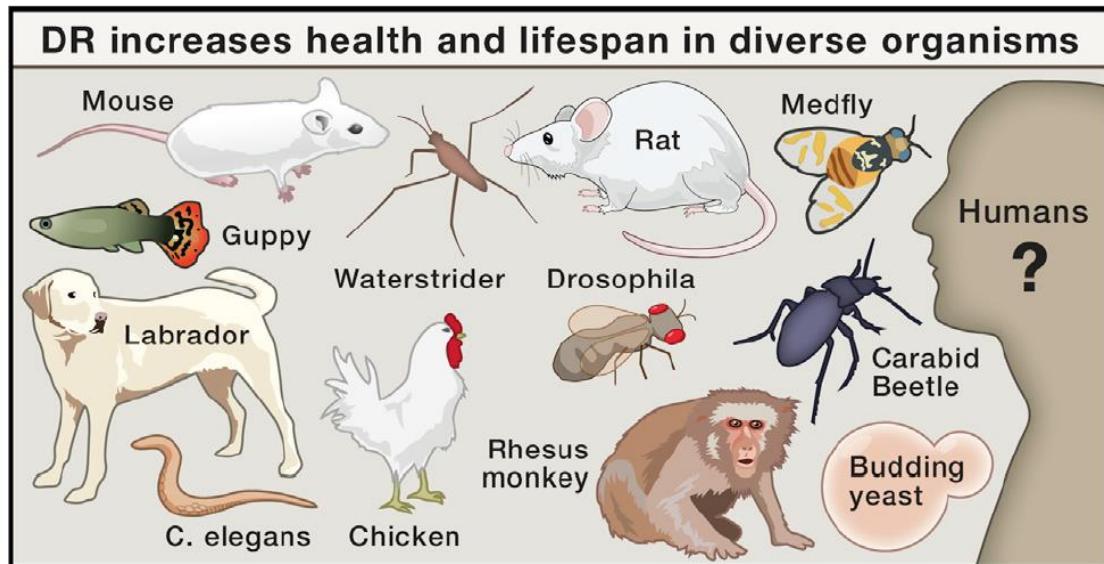
Capacités
intrinsèques
et réserves

Industriels (IOT, Thalès, Sigfox, La Poste, Orange, Airbus, Ind. Pharma.)

Réparation, cicatrisation et régénération

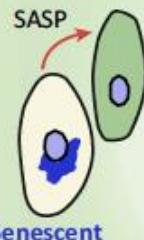


Médecine régénératrice: le futur



Remaining fundamental and translational challenges

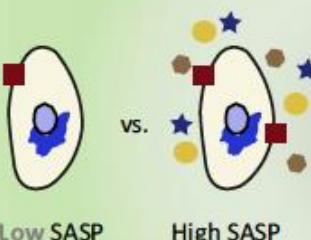
(A) How does SASP impair neighboring cells?



- Altered stress signaling?
- DNA-damage response?
- Stemness/differentiation?



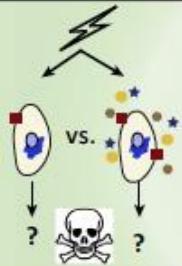
(B) What causes senescence/SASP heterogeneity?



- Random
- Circadian rhythms
- Cell cycle state prior to induction
- Differences in protein stress
- Extrinsic stimuli



(c) Can therapies selectively target senescent subpopulations?



No: Golden bullet against all senescence?

Yes: Can this be steered?

Disease-specific therapies?



(d) Criteria for antiaging therapies?



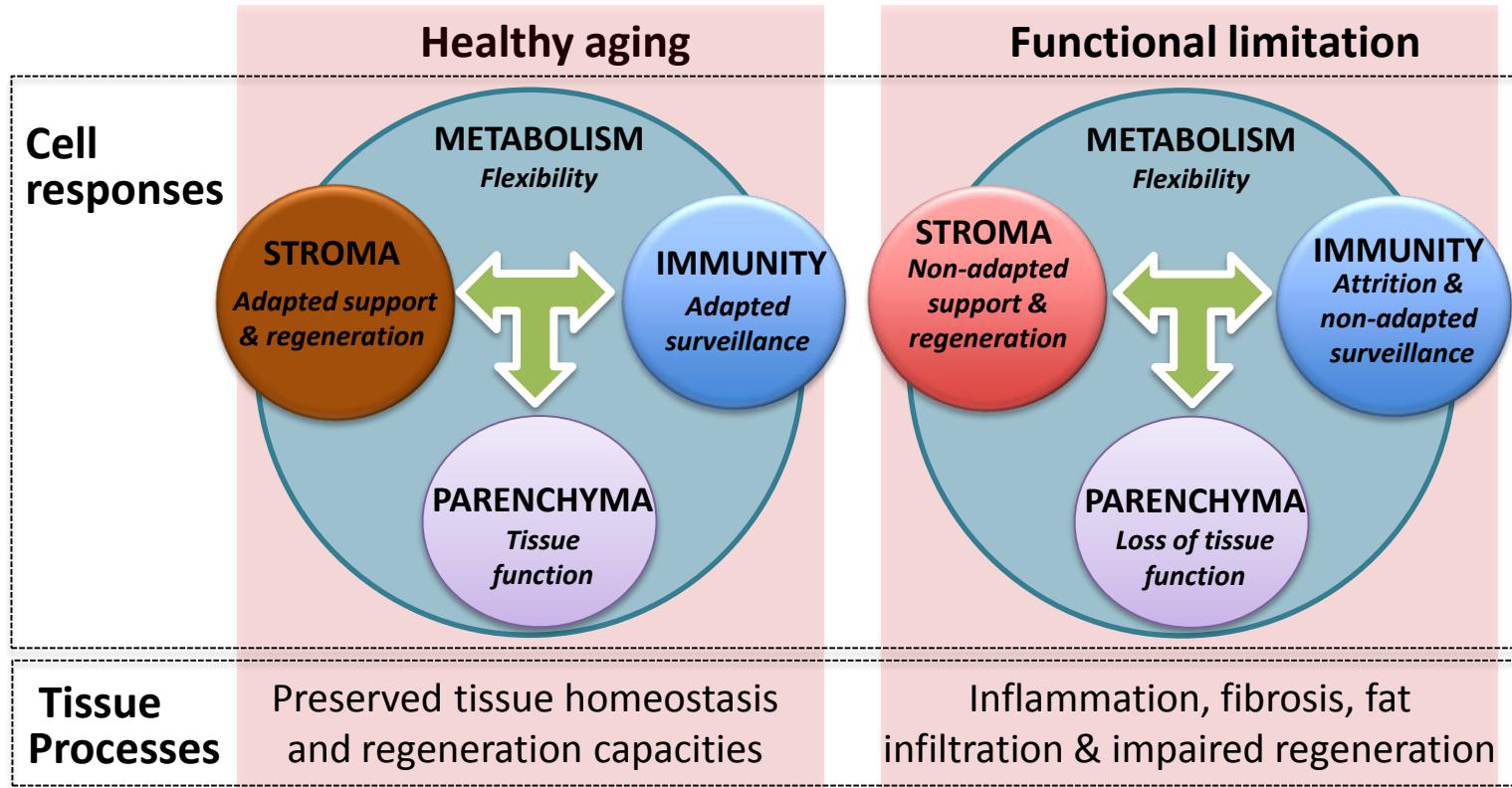
More than for immediate life-threatening diseases these criteria need to be met:

- Very low off-target toxicity
- Low cost of goods
- Favorable administration regimens



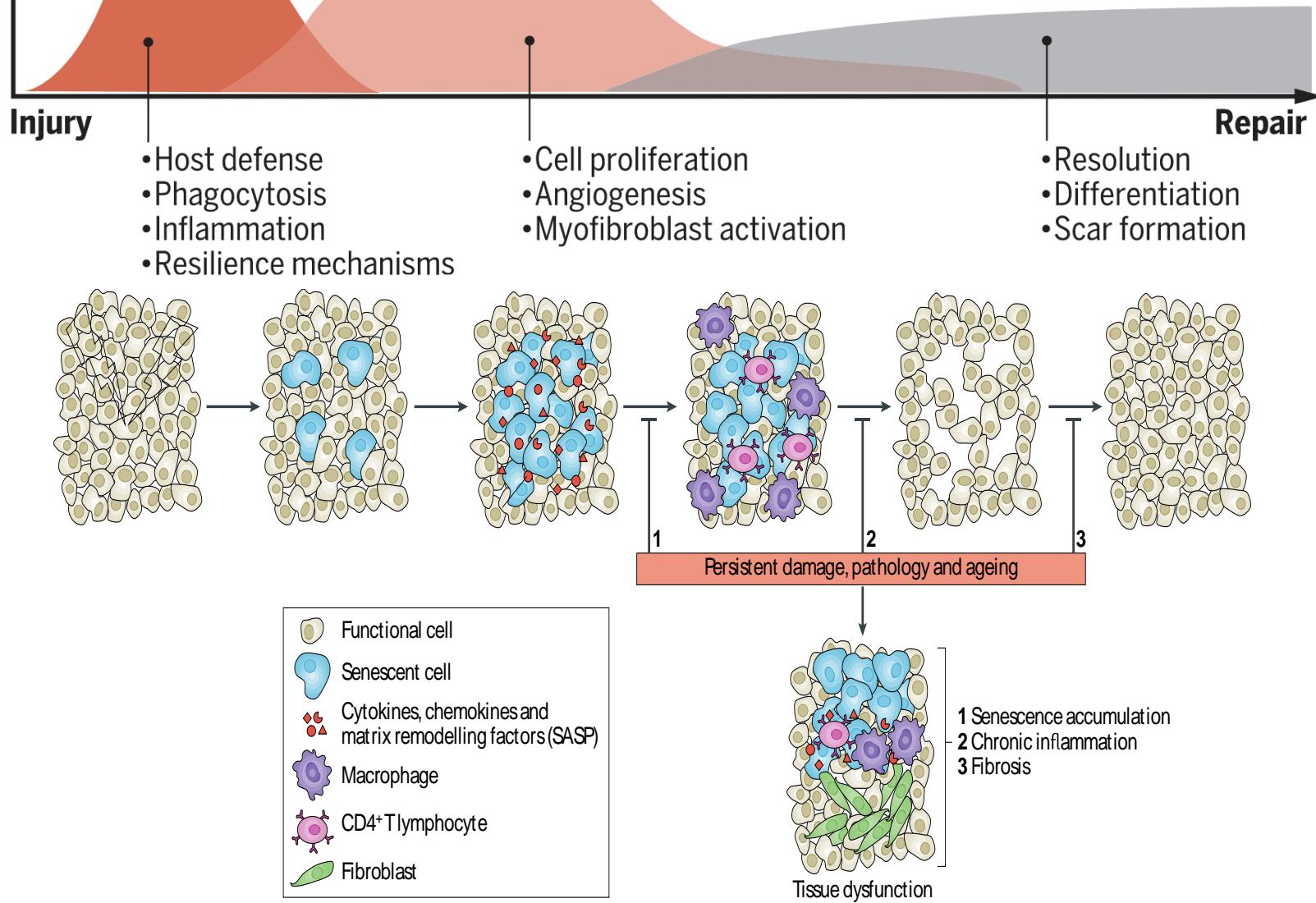
Médecine régénératrice

le rationnel: Le vieillissement comme une cicatrisation évolutive à l'échelle de l'organisme



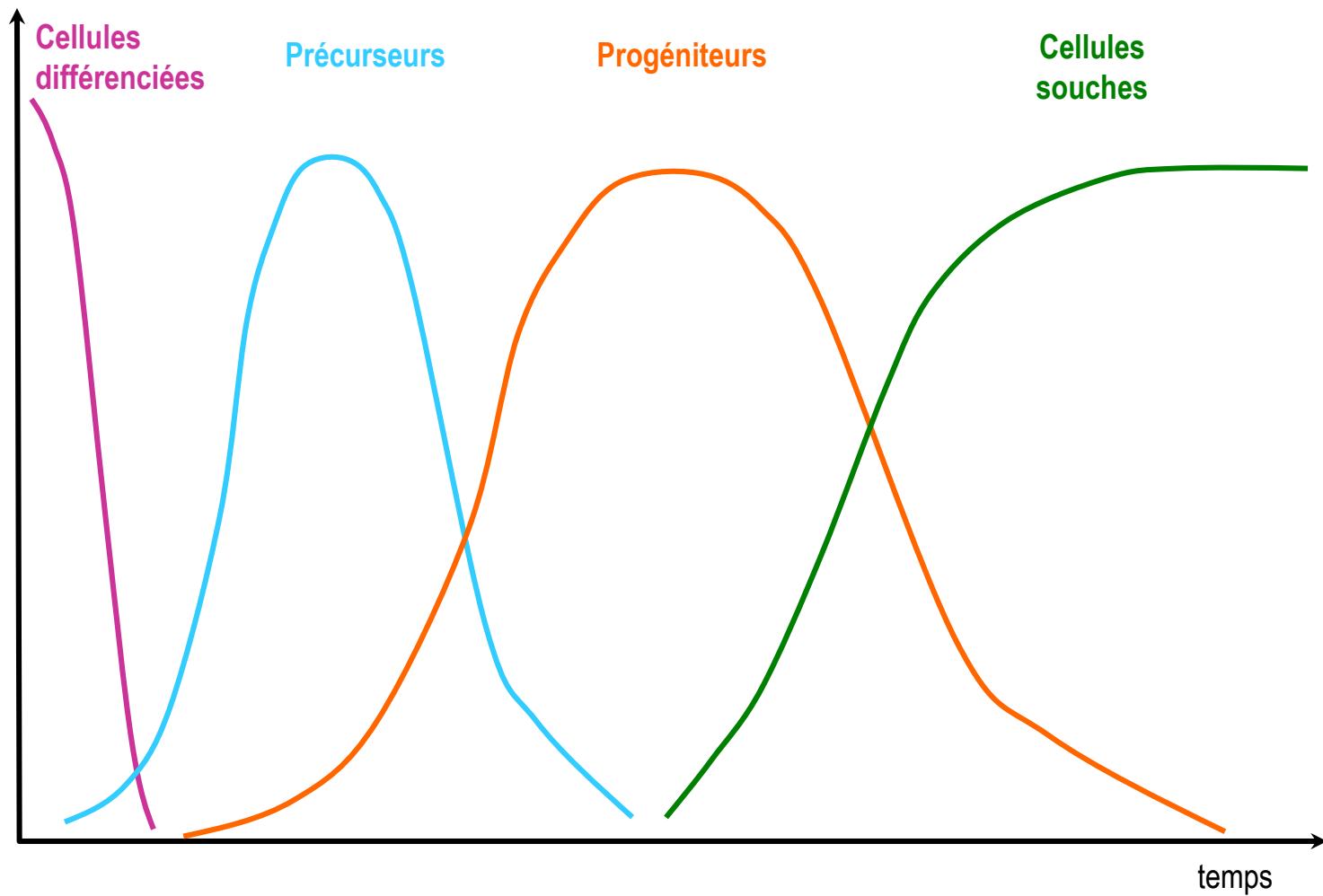
Repair mechanisms

Eming et al., *Science* **356**, 1026–1030 (2017)



Pourquoi les cellules souches ?

Restauration
fonctionnelle



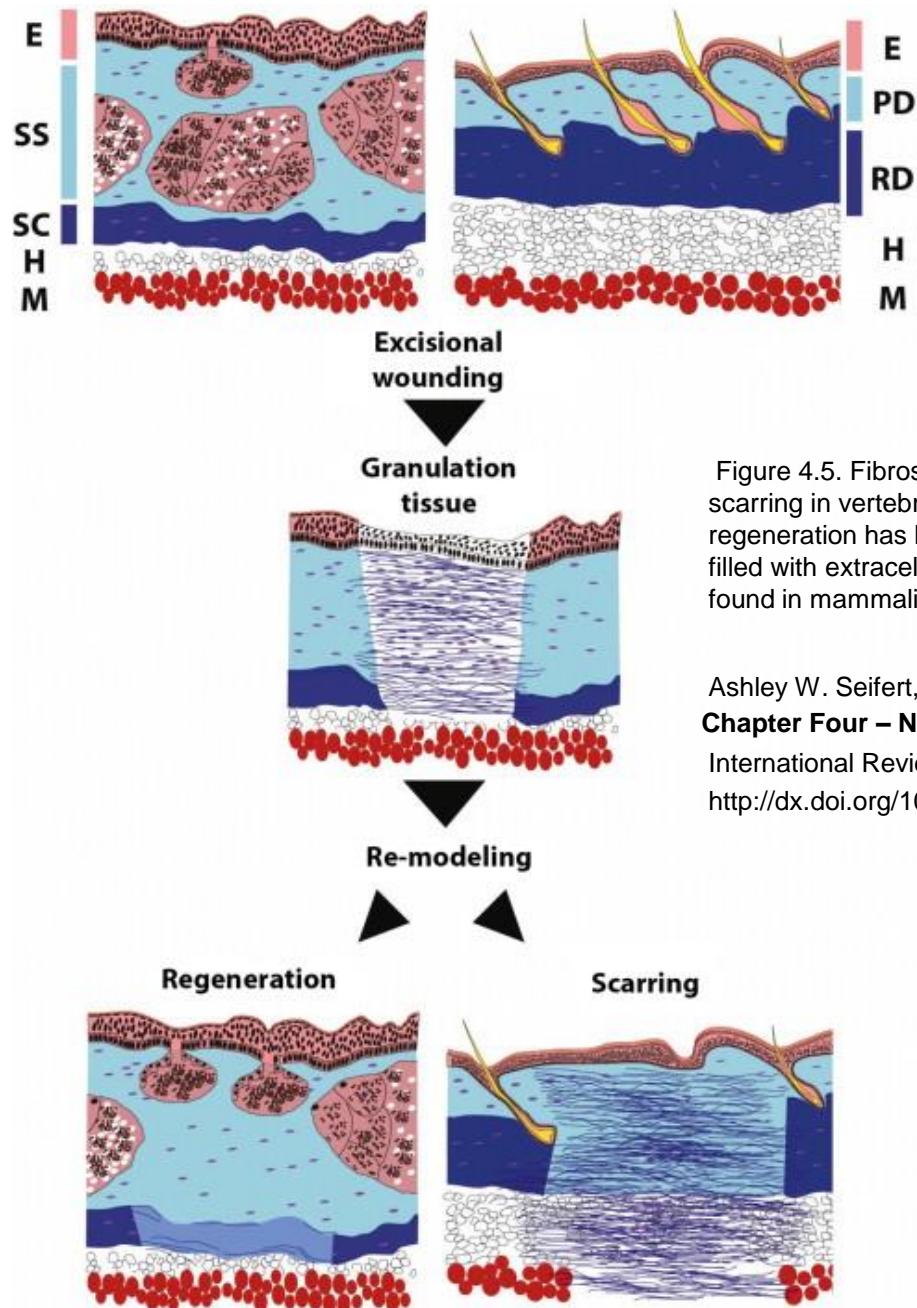


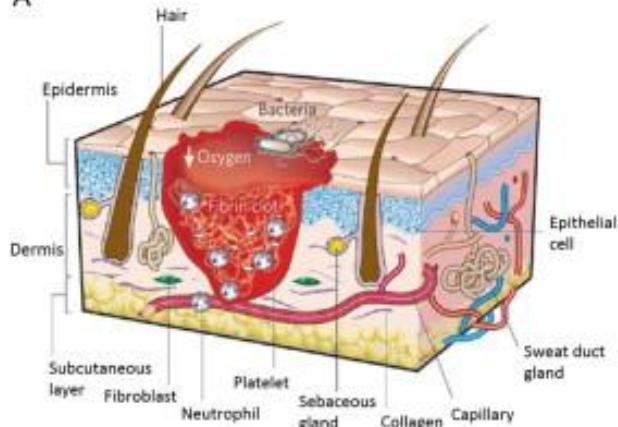
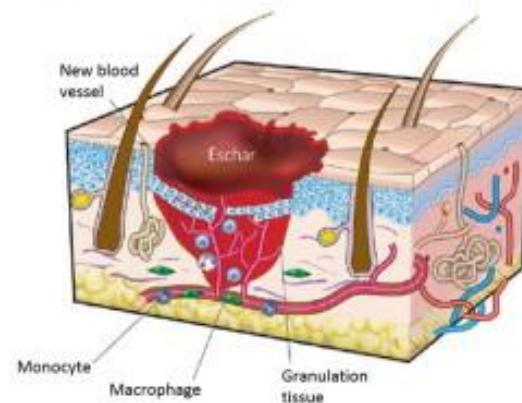
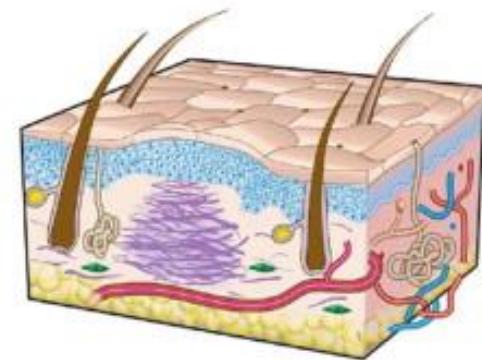
Figure 4.5. Fibrosis precedes both regeneration and scarring in vertebrates. In adult vertebrates where skin regeneration has been described, the wound bed becomes filled with extracellular matrix resembling granulation tissue found in mammalian wounds that sc...

Ashley W. Seifert, Malcolm Maden

Chapter Four – New Insights into Vertebrate Skin Regeneration

International Review of Cell and Molecular Biology, Volume 310, 2014, 129–169

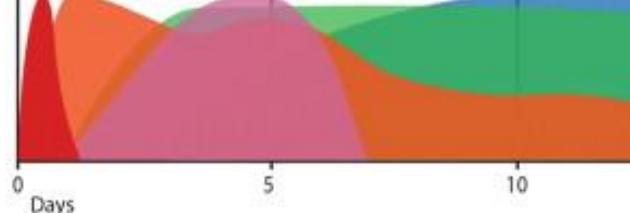
<http://dx.doi.org/10.1016/B978-0-12-800180-6.00004-9>

A**B****C**

Injury

Inflammation

Hemostasis
Inflammation
Re-epithelialization
ECM deposition



Tissue formation

Contraction

scar formation

15

20

25

3

6

9

12

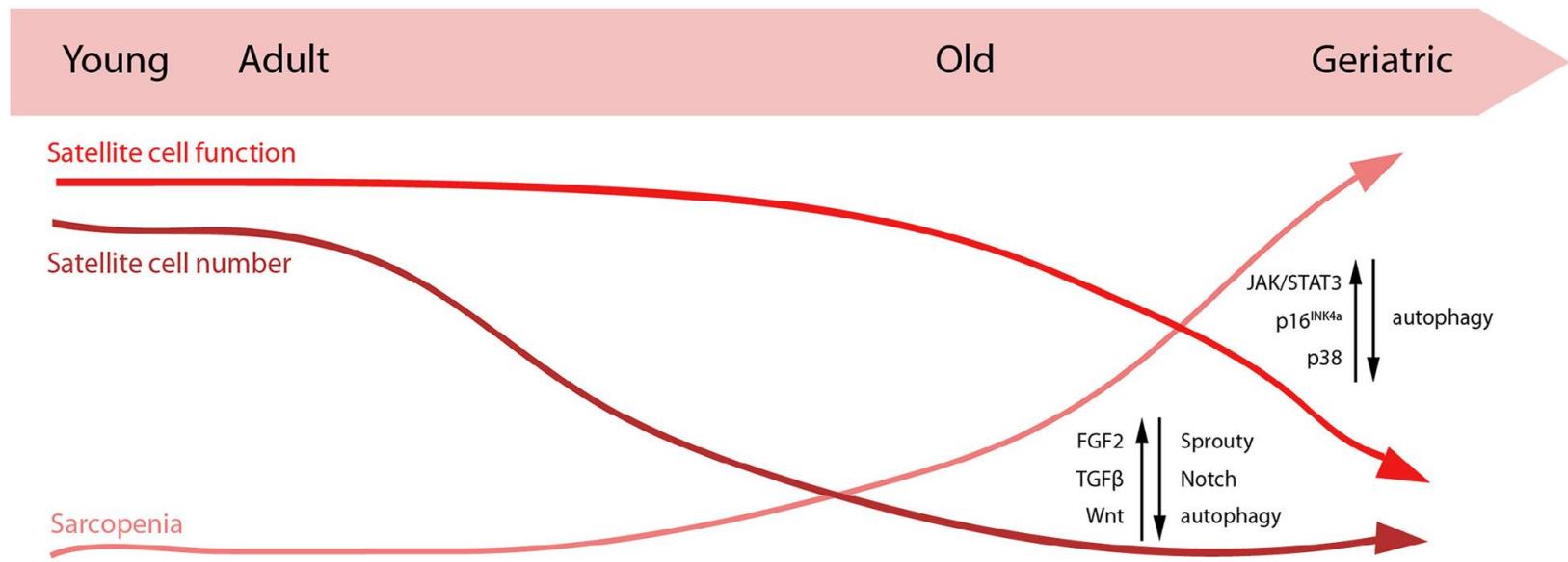
Tissue remodeling

Scar remodeling

Scar persists

Days

Seifert et Maden, **Chapter Four – New Insights into Vertebrate Skin Regeneration**. International Review of Cell and Molecular Biology, Volume 310, 2014, 129–169



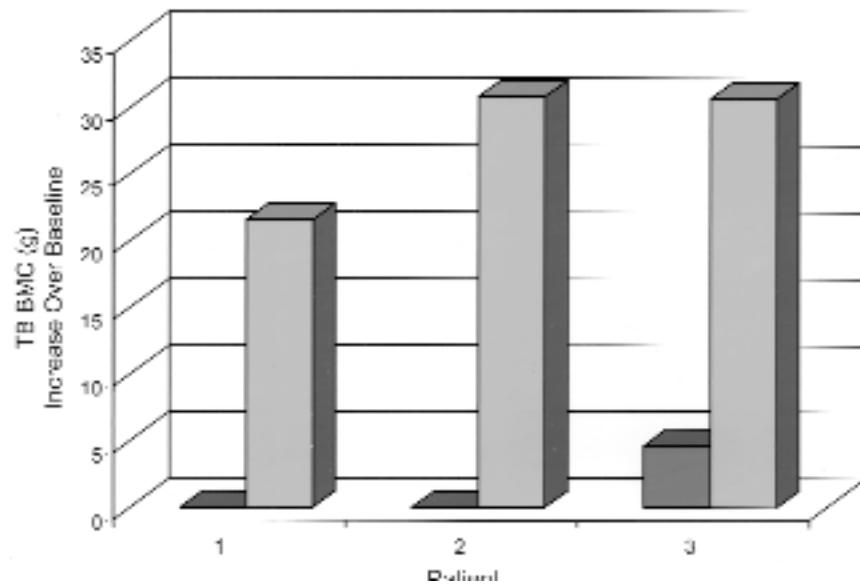
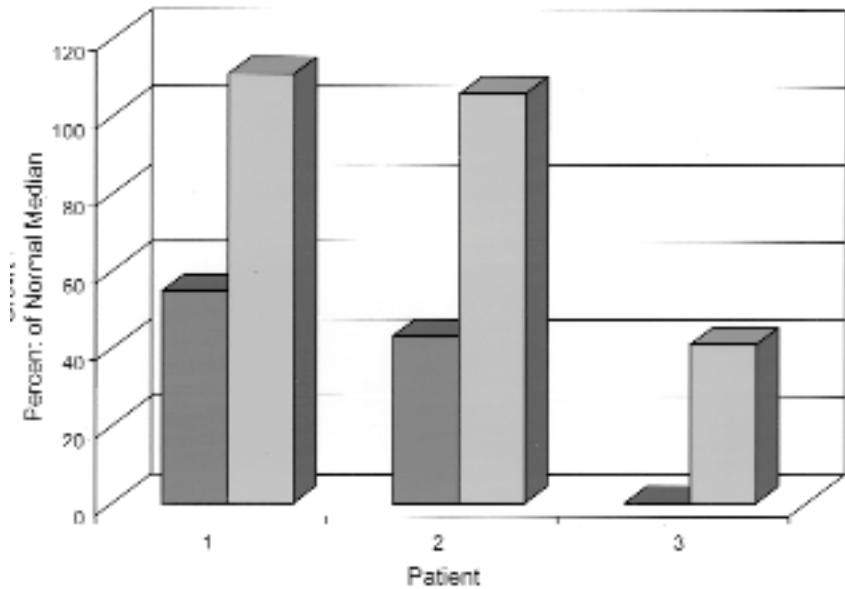
Pedro Sousa-Victor ^a, Pura Muñoz-Cánores [Molecular Aspects of Medicine 50 \(2016\) 109–117](#)

Régénération et Médecine régénératrice

Transplantability and therapeutic effects of bone marrow-derived mesenchymal cells in children with osteogenesis imperfecta

NATURE MEDICINE • VOLUME 5 • NUMBER 3 • MARCH 1999

EDWIN M. HORWITZ¹, DARWIN J. PROCKOP², LORRAINE A. FITZPATRICK³,
WINSTON W. K. KOO⁴, PATRICIA L. GORDON¹, MICHAEL NEEL¹, MICHAEL SUSSMAN⁵,
PAUL ORCHARD⁶, JEFFREY C. MARX¹, REED E. PYERITZ² & MALCOLM K. BRENNER¹



Régénération et mammifères

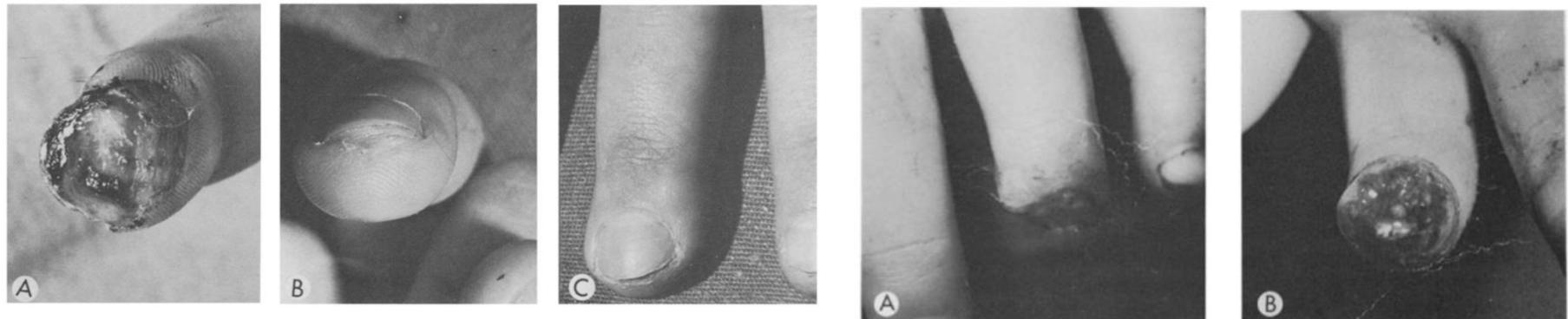


Fig. 2. (A) Amputation of finger tip in 5-yr-old girl. (B), (C) Twelve weeks after accident.

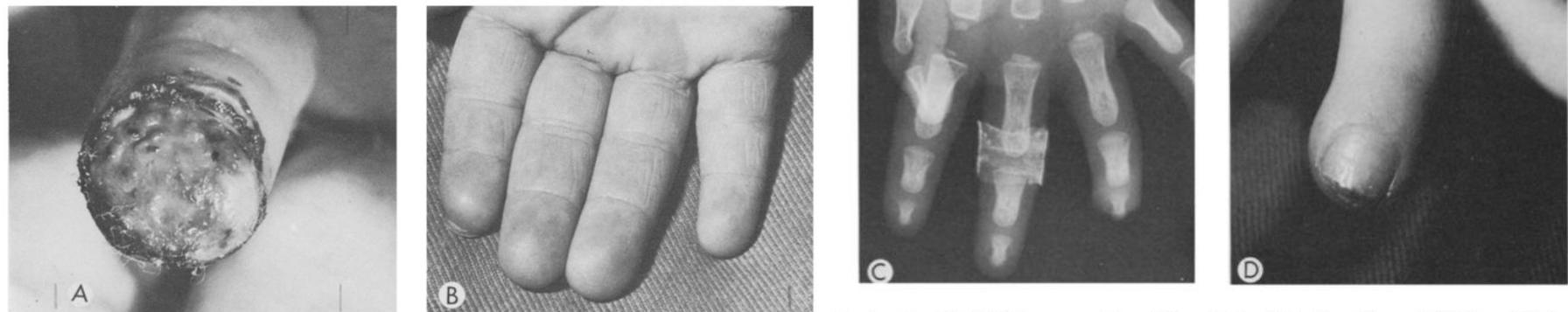


Fig. 1. (A), (B) Guillotine amputation of finger tip in child of 1 yr 10 mo. (C) X-Ray. (D) Eleven weeks after accident.

Fig. 3. (A) Amputation of finger tip in child of 1 yr. (B) Three years Later—Child now aged 4 yr.

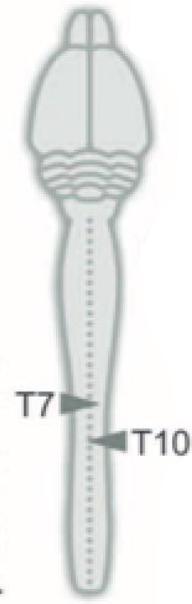
Cynthia M. Illingworth

Journal of Pediatric Surgery, Vol. 9, No. 6 (December), 1974

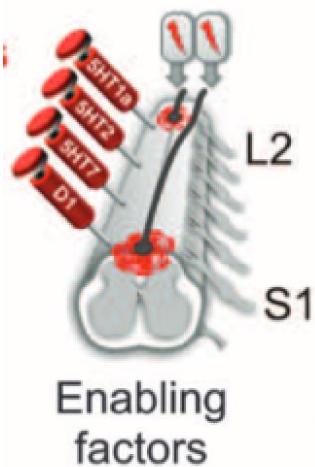


Restoring Voluntary Control of Locomotion after Paralyzing Spinal Cord Injury

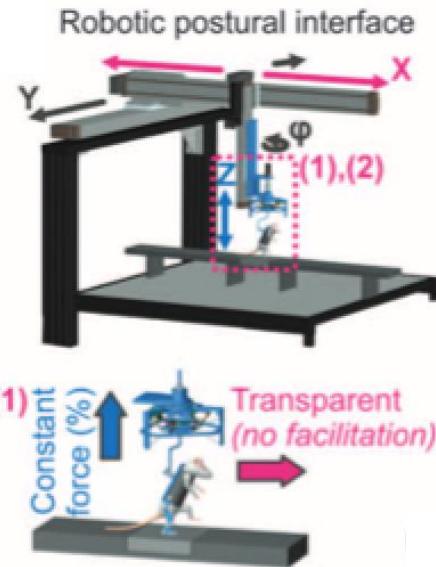
Rubia van den Brand,^{1,2*} 1 JUNE 2012 VOL 336 SCIENCE



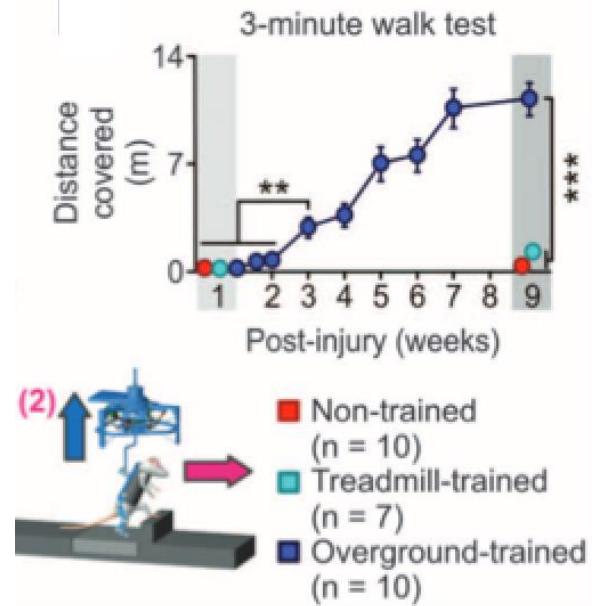
Agression
Perte de fonction



Facteurs
permissifs
initiaux



« Aide à » évolutive

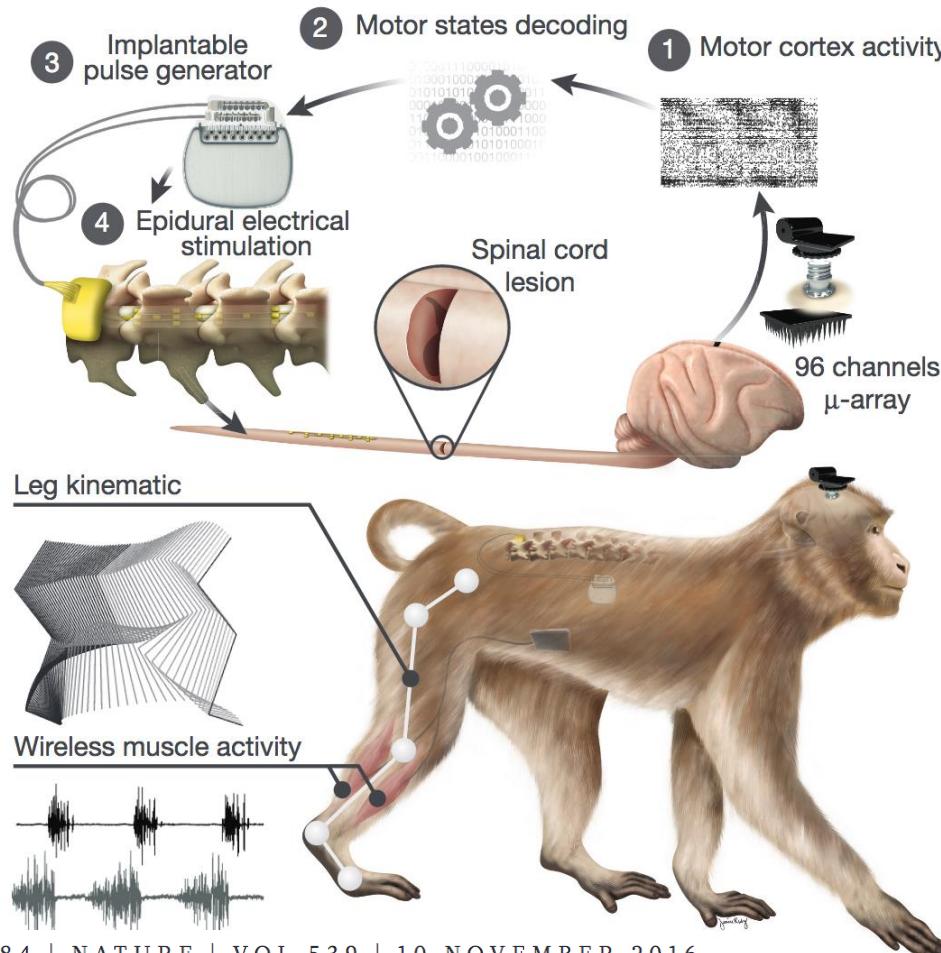


Restauration
de fonction

Régénération et Médecine régénératrice

A brain–spine interface alleviating gait deficits after spinal cord injury in primates

Marco Capogrosso^{1,2*}, Tomislav Milekovic^{1*}, David Borton^{1,3*}, Fabien Wagner¹, Eduardo Martin Moraud², Jean-Baptiste Mignardot¹, Nicolas Buse⁴, Jerome Gandar¹, Quentin Barraud¹, David Xing³, Elodie Rey¹, Simone Duis¹, Yang Jianzhong⁵, Wai Kin D. Ko⁵, Qin Li^{5,6}, Peter Detemple⁷, Tim Denison⁴, Silvestro Micera^{2,8}, Erwan Bezard^{5,6,9,10}, Jocelyne Bloch¹¹ & Grégoire Courtine^{1,11}



ASC & «aging» ?

Regenerative medicine ⇔ age related diseases

Aging ⇔ unbalanced cell turn-over & tissue homeostasis

Aging & stem cells ⇔ exhaustion of regenerative cells pool

and/or decrease of proliferation potential

and/or decrease of multipotency/plasticity

and/or decrease of their paracrine activity