Stem Cell Therapy as Medical Coutermeasures for external radiation burns

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Specificity of the Radiological Burn

- The « Radiological Burn » is a dynamic process
- Unpredictable evolution with successive inflammatory waves
- Pain +++ resistant to the classical drugs
- The occurrence of pain is a clinical symptom annoucing a new wave of recurrence.

Past Practical :
Therapeutical Approaches of the Radiological Burn

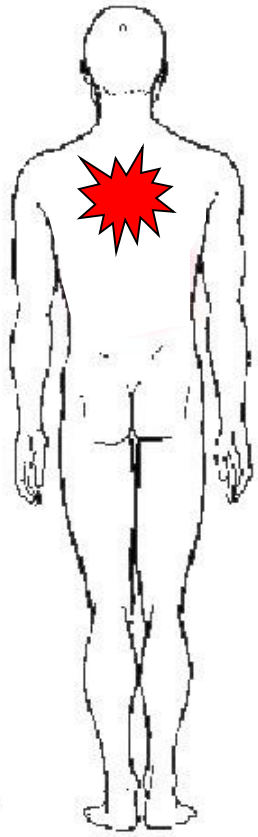
- "Wait and See" clinical approach : Wait the maximal extension of the lesions before surgery
- In case of superficial lesions of distal extremities, limited excision with conservative surgery
- In cases of profound and large necrosis, lesion should be excised and wound bed should be covered with a good quality, full-thickness skin graft.
- In case of painful deep ulcerations and necrosis, classical techniques of plastic surgery (ulcerectomy, necrectomy, wound closure by rotation flap, amputation)

Repetitive courses of surgical treatment

Medical Countermeasure for radiation-induced burn

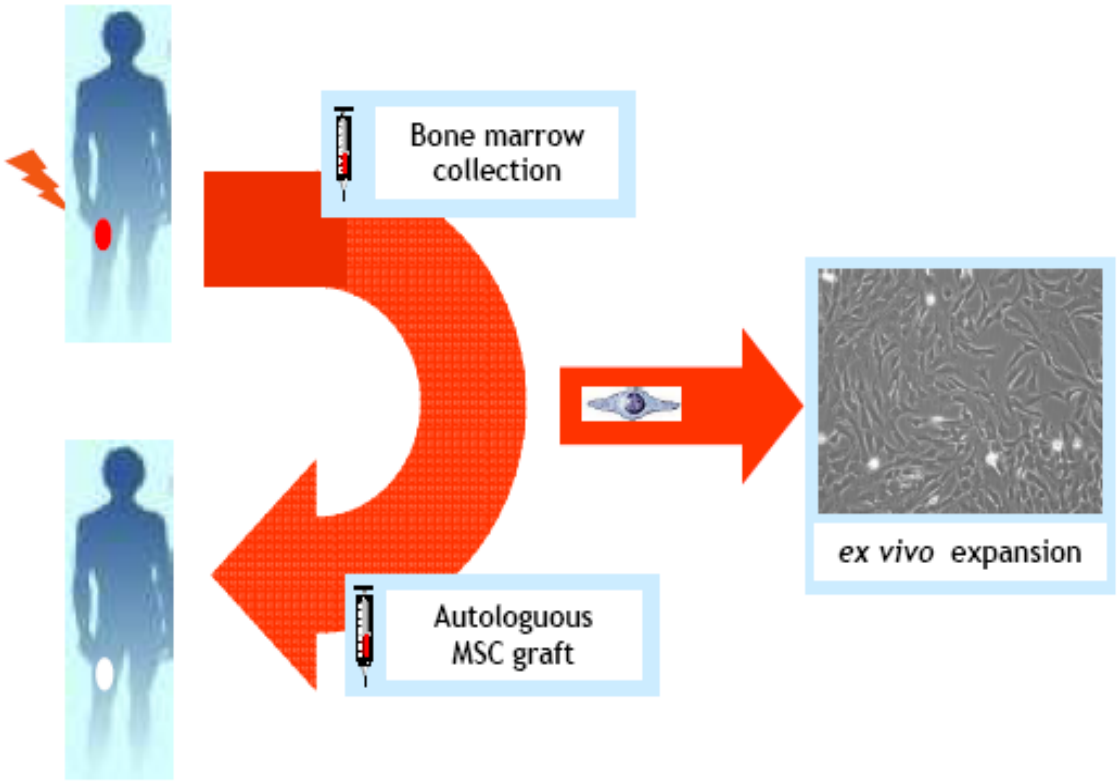
Cutaneous Radiation syndrome
back

After 4 excisions, 5 skin autograft and one omentum flap,
day 500 p.i., final aspect



Hospitalization in France (at day 88), in the Burn Treatment Department (HIA Percy), le 23th December 2001.

New approach by Mesenchymal Stem Cell Therapy

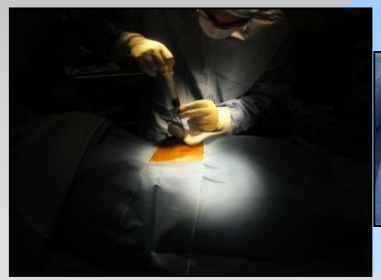


stem cell injection have the capacity to acquire morphology and function of the deficient cells after tissue damage.

Autologous human grade MSC production

Safe closed system

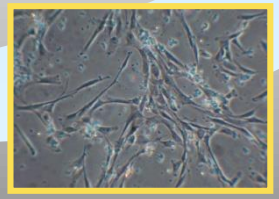
1) MSC Production



2) MSC collection

3) MSC culture

stem therapy unit
(CTSA-Percy hospital)

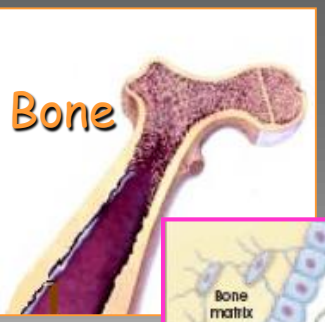


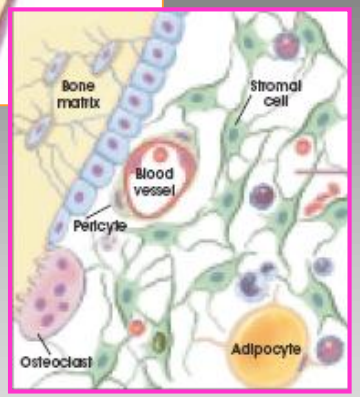
10 days

4) quality controls
(Sterility, Phenotype,
CFU-F, Numération, karyotype)

5) MSC
injection

MSC are multipotent and exhibit stromal cell properties





Normoxia

Hypoxia
Ca^{++}

Vascular Niche

Cytokines
(Tpo, SCF, HGF, FGF4...)

Osteoclasts

Proteases
(MMP9, CTK...)

VLA-4/VCAM-1
Ang-1/Tie2
Wnt/Beta-Catenin
Jagged-1/Notch..

CAR cells

ESC

HSC

ECM
(OPN)

Chemokines
(SDF-1, Il-8..)

MSC

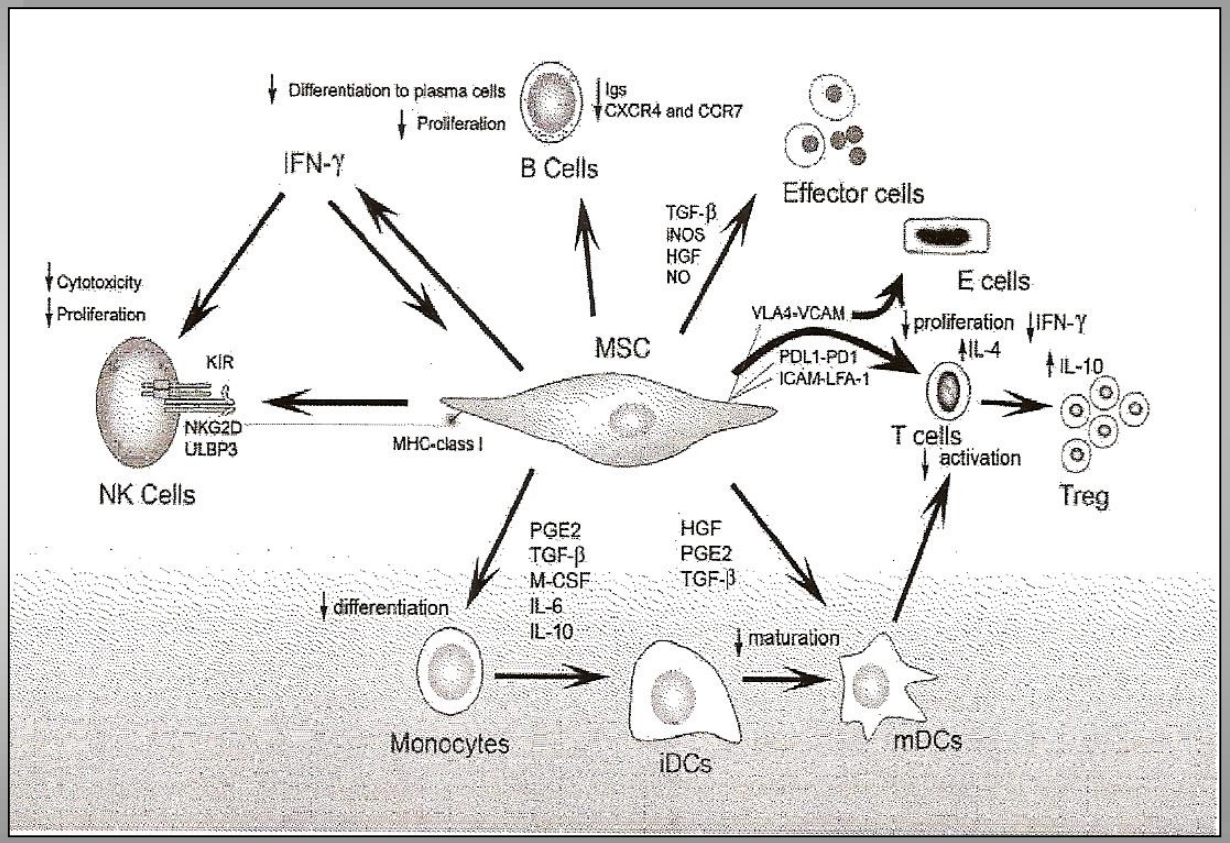
Osteoblasts

Fibroblasts

Adipocytes

Endosteal Niche

Immuno-modulatory effect of MSC



- ✓ Inhibition of T and B Lymphocyte proliferation and activation
- ✓Inhibition of Dendritic cell and NK cell proliferation and differentiation
- ✓role of TGFβ, HGF and PGE2 and Indoleamine Dioxygenase

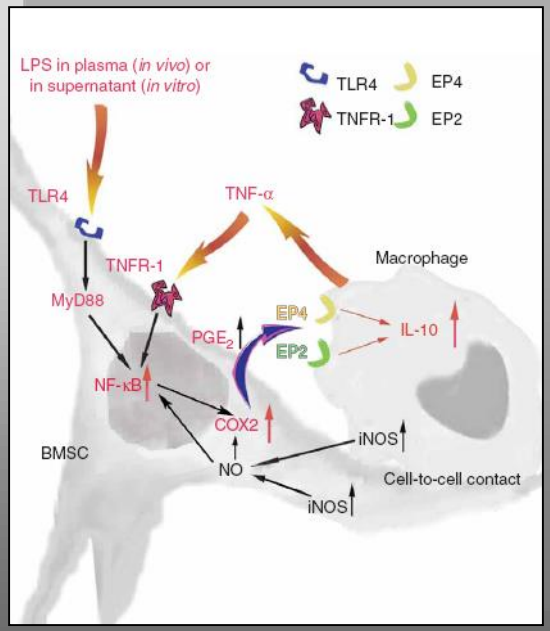
(Tse et al., Transplantation, 2003; Krampera et al., Blood, 2003; Di Nicola et al., Blood, 2002; Meisel et al., Blood, 2004; Glennie et al., Blood, 2005; Jiang et al., Blood, 2005; J. A. Kode et al., Cytotherapy, 2009)

Antiseptic activity of MSCs

Bone marrow stromal cells attenuate sepsis via prostaglandin E_2–dependent reprogramming of host macrophages to increase their interleukin-10 production

Krisztián Németh[1,6], Asada Leelahavanichkul[2,6], Peter S T Yuen[2], Balázs Mayer[1], Alissa Parmelee[1], Kent Doi[2], Pamela G Robey[1], Kantima Leelahavanichkul[1], Beverly H Koller[4], Jared M Brown[5], Xuzhen Hu[2], Ivett Jelinek[3], Robert A Star[2,6] & Éva Mezey[1,6]

Nemeth K *et al.*, Nature Med, Vol 15, Numb 1 2009



Endotoxin and circulating TNFα activate MSC via TLR4 and TNFR1

MSC produce **PGE2**

↓

Activation of IL10 production by macrophages

Mesenchymal Stem Cell: Drug Cell?

Immunomodulatory effect:

Prevention and treatment of GVH (Inhibition of T Ly prolif : rôle of TGF beta HGF and IDO)

Anti-inflammatory

Anti-fibrotic and antiseptic activities:

Animal models of Ischemia /Reperfusion, of kidney and myocard (modulation of pro- et anti-inflammatory cytokines, rôle of antagonist IL1R)

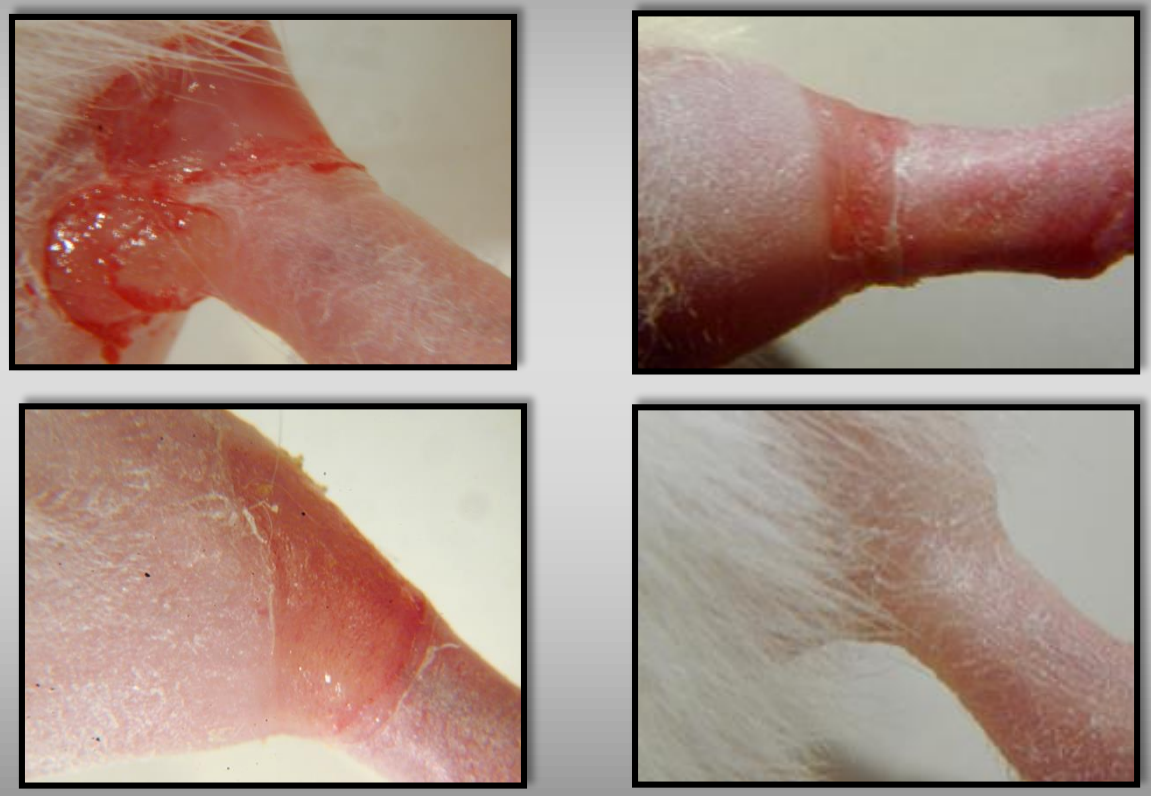
Multipotent properties:

Bone, vessel, muscles…

Good Candidate for Injured Tissue Repair

[Glennie et al., Blood, 2005] *[Ortiz et al., PNAS, 2007]* *[Kim et al., Clin Cancer Res 2005]*

Preclinical studies of Radiation burns in NOD/SCID mouse model

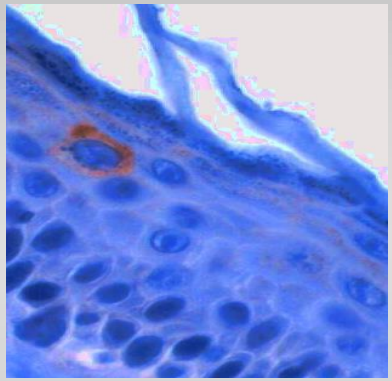


(Francois et al., *Annals Hemat.*, 2007)

Mechanism

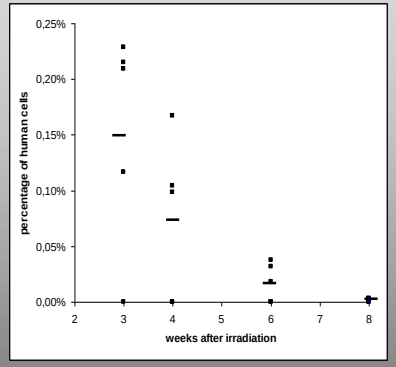
- MSC induce
  Wound healing
  Muscle regeneration
  = Functional recovery

- Selective MSC implantation in the irradiated area
  Low differentiation capacity
  Low proliferation capacity
  Paracrine effect (inflammation modulation, anti-fibrotic, pro-angiogenic)



- Clinical protocols

Optimal MSC concentration : $2.10^6 kg^{-1}$ Repetitive injection>single injection
Local injection = systemic injection
Preventive injection = curative injection
Frozen CSM ≤ fresh CSM



MSC therapy of Radiation burns

Accidental irradiation burn (Chile 2005)

D+18 PI
Ulceration & necrosis

D+25 PI
Blistering

D+42 PI moist desquamating burn lesion

[Lataillade J-J et al., Regen. Med. 2007]

Local MSC administrations + surgery

Skin autograft

+

Autologous MSC (Passage 1)

($76x10^6$ at D90 PI)

Excision of necrotic tissues

+ Skin autograft

+ $400x10^6$ Autologous MSC

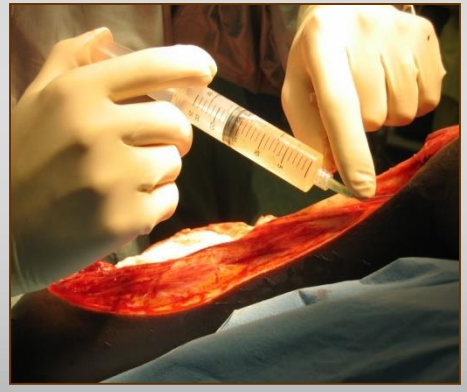
(P1: $168x10^6$ at D90 PI and P2: $226x10^6$ at D99 PI)

MSC therapy of Radiation burns

Accidental irradiation burn (Senegal 2007)

D+170 PI
Ulceration & necrosis

Excision of necrotic tissues



5 MSC administrations were performed at D191-D200-D226-D239 and D268 PI:

800.10^6 MSC

Latissimus dorsi muscle flap

Skin autograft

[Bey E and Lataillade J-J, Wound Rep. Regen. 2010]

RESULTS

1st case

7 YEARS PI
without relapse

2nd case

5 YEARS PI
without relapse

Clinical success

	Lesion characteristics					Clinical criterion of Mesenchymal Stem Cell therapy					
		localisation	severity Metrepol	surface > 20 - 25 Gy	dose (Gy)	route of injection	number of cell injected	MSC origin	number of injection	combined treatment	
Patient 1 (Chili 2005)		Left hand	IV	40 cm^2	31[a]	Local	76.10^6	autologous	1	Skin autograft	
Patient 1 (Chili 2005)		Left buttock	IV	80 cm^2	2000[c]	Local	386.10^6	autologous	2	Surgery	
Patient 2 (Sénégal 2007)		Left arm	IV	250 cm^2	53.5[a]	Local	761. 10^6	autologous	5	Surgery	
Patient 3 (Tunisie 2008)		Left hand	IV	100 cm^2	38[a]	Local	406.10^6	autologous	2	Skin autograft	
Patient 4 (Equateur 2009)		Right leg	IV	400 cm^2	4200[c]	Local	1238.10^6	autologous	6	Surgery	
Patient 5 (FJ) (Vénézuéla 2010)		Left and right hand	IV	100 cm^2	40[a]	Local	260.10^6	autologous	5	Skin autograft	
Patient 6 (EB) (Gabon 2010)		Left hand	IV	30 cm^2	35[b]	Local	76.10^6	autologous	2	Skin autograft	
Patient 7 (FR) (Chili 2011)		Right foot	IV	20 cm^2	23[a]	Local	18. 10^6	autologous	1	Surgery	

a: EPR dose evaluation (bone), b: EPR dose evaluation (nail), c: physical dose reconstruction (contact dose at the skin)

Possible improvements…

CONCLUSION : New Therapeutical Approaches of the Severe Radiological Burn

multidisciplinary therapeutic approach

- Rapid medical intervention before the occurrence of the radionecrosis
- Numerical dosimetry guided surgery and EPR dosimetric assessment
- Large volume of necrotic tissue requires association of surgery with stem cell therapy
- Small volume (extremities) may be managed only with local and repetitive Mesenchymal Stem Cell injections

Medical breakthrough in the treatment of irradiated tissue!

MERCI !

IRSN

Pr Gourmelon,
Drs Bottellier, Roy, Chapel, Benderitter…

CTSA

Pr Joussemet
Pr Lataillade
Dr Prat,
I Ernou, M Gourven,
F Tissedre L Boutin,
C Ait-Mansour

HIA PERCY

Hématologie
Pr De Revel

Chirurgie plastique
Pr Bey,Drs Pradier, Duhamel, Fossat

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Dr Carsin
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