ANGIOGENÈSE THÉRAPEUTIQUE

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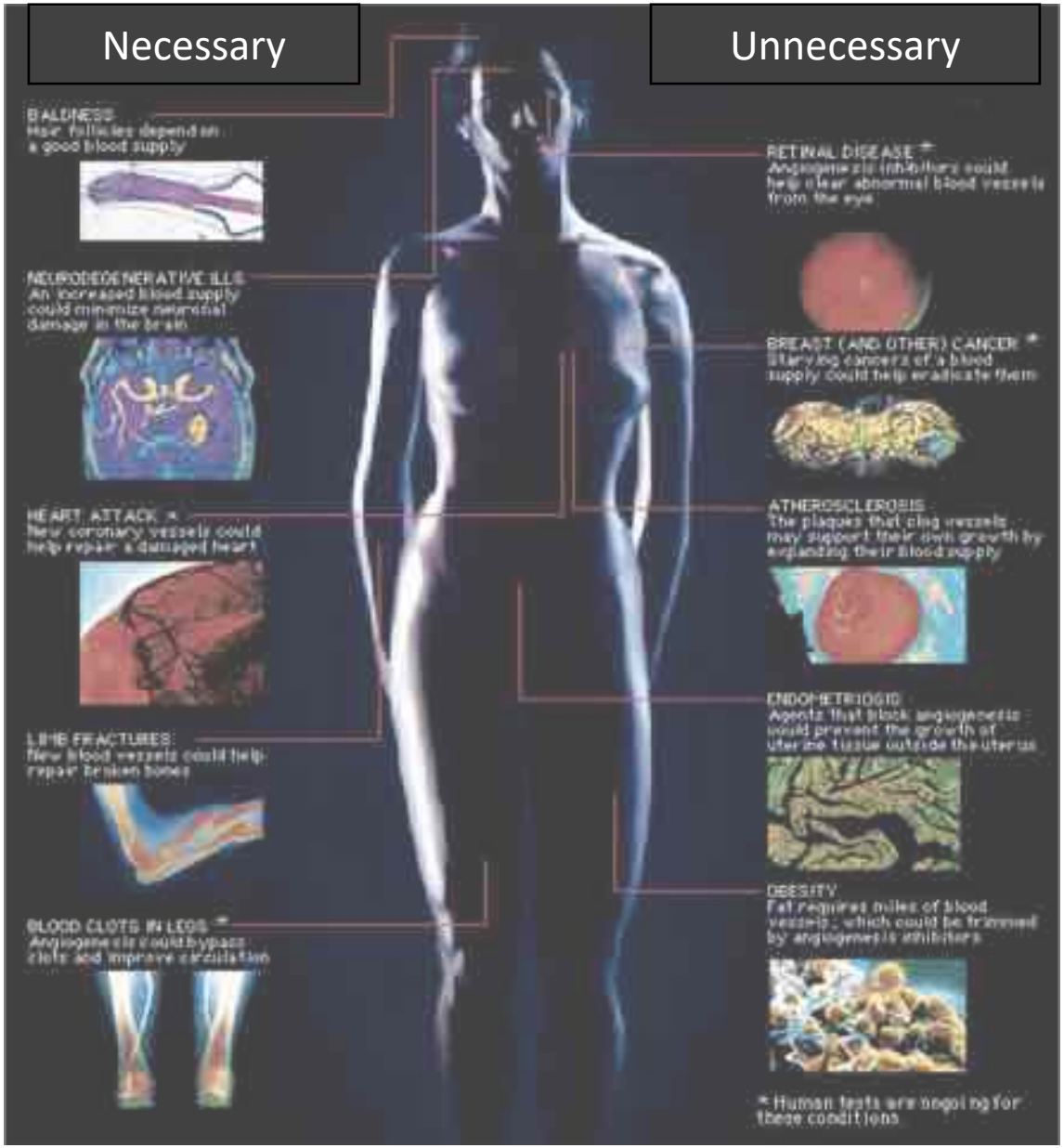
Université de Paris

Angiogenèse thérapeutique



Inhibition

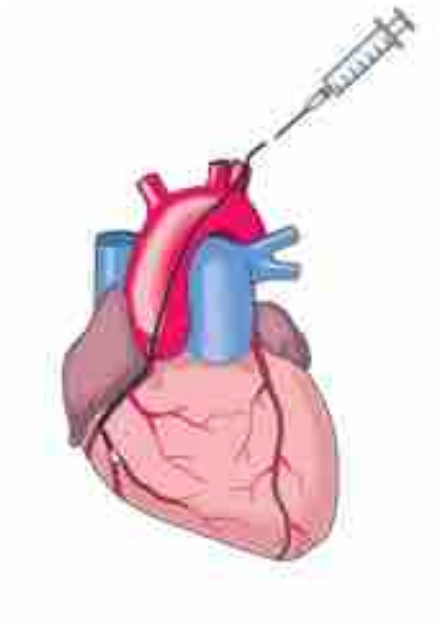
- Hémangiomes
- Psoriasis
- Rétinopathie
- Arthrite rhumatoïde
- Athérosclérose
- Croissance tumorale et Métastase

Activation

- Pathologie ischémique
  - Ischémie myocardique
  - Ischémie périphérique
  - Ischémie cérébrale
- Cicatrisation
- Chirurgie reconstructive

Angiogenèse thérapeutique et pathologies cardiovasculaires ischémiques

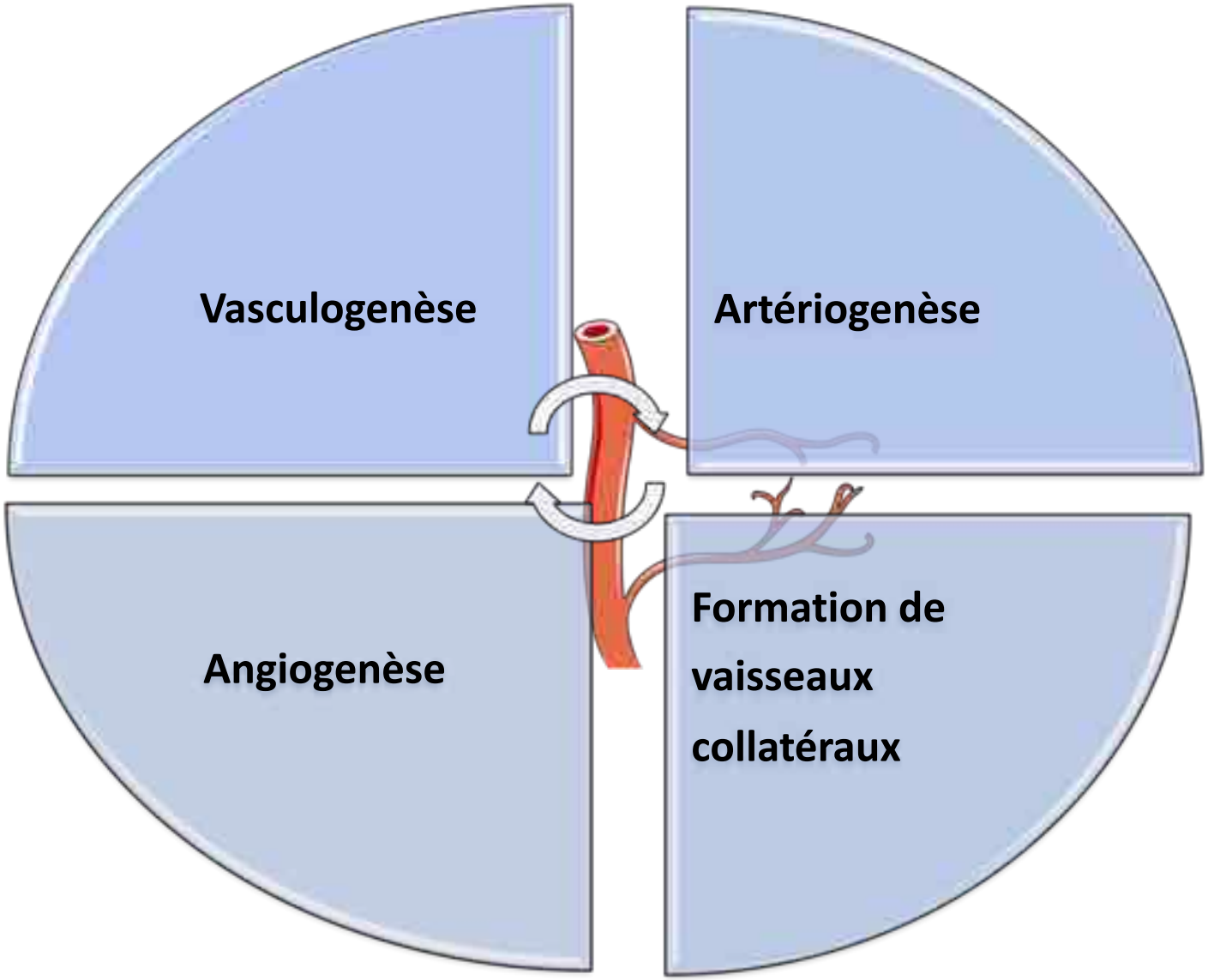
Pathologies ischémiques cardiaques:
Infarctus aigu, Insuffisance cardiaque



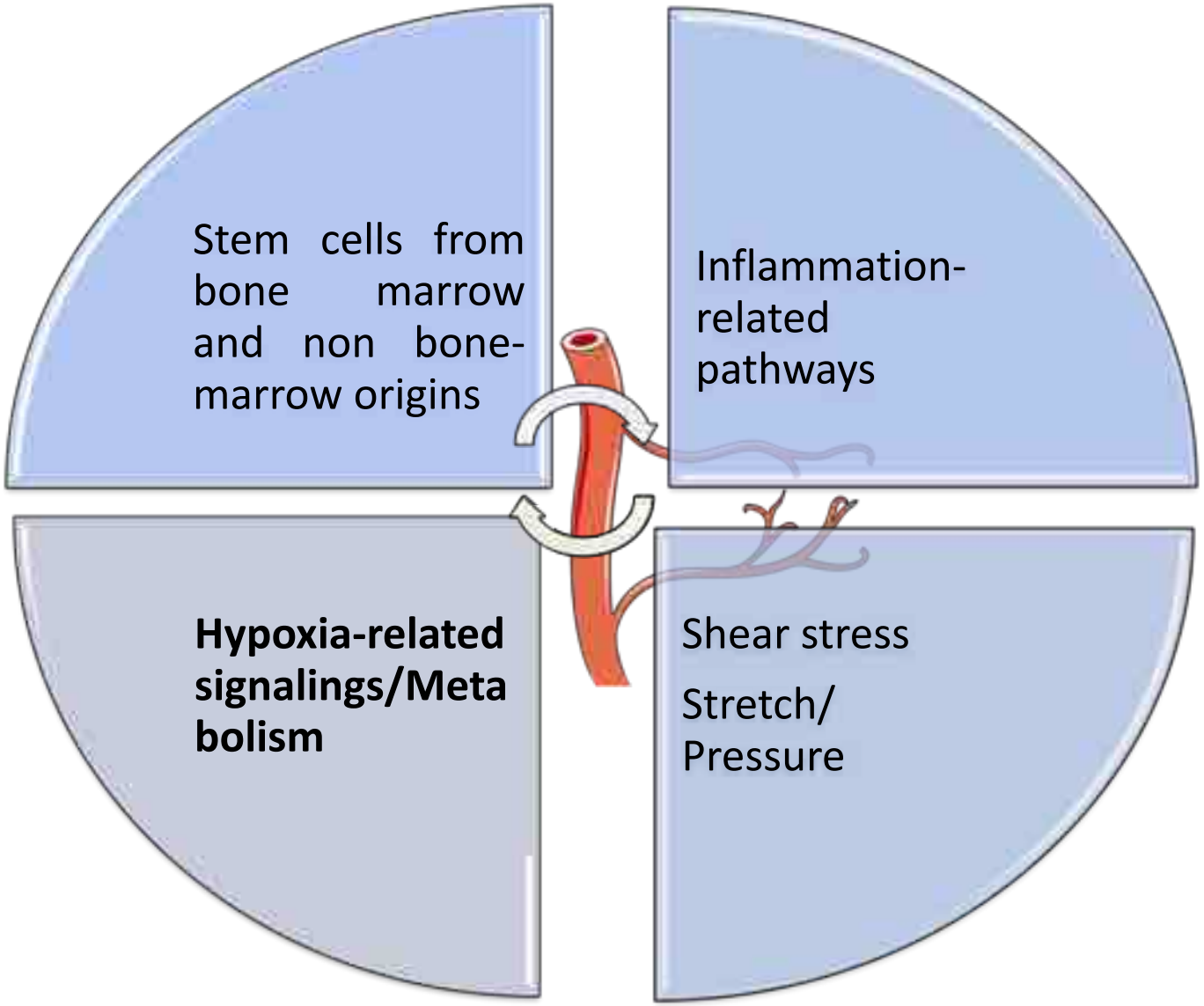
Pathologies ischémiques vasculaires (non coronaire):
Ischémie critique du membre inférieur
Artérite Oblitérante du membre inférieur

Objectifs thérapeutiques: stimuler la revascularisation/perfusion de la zone lésée

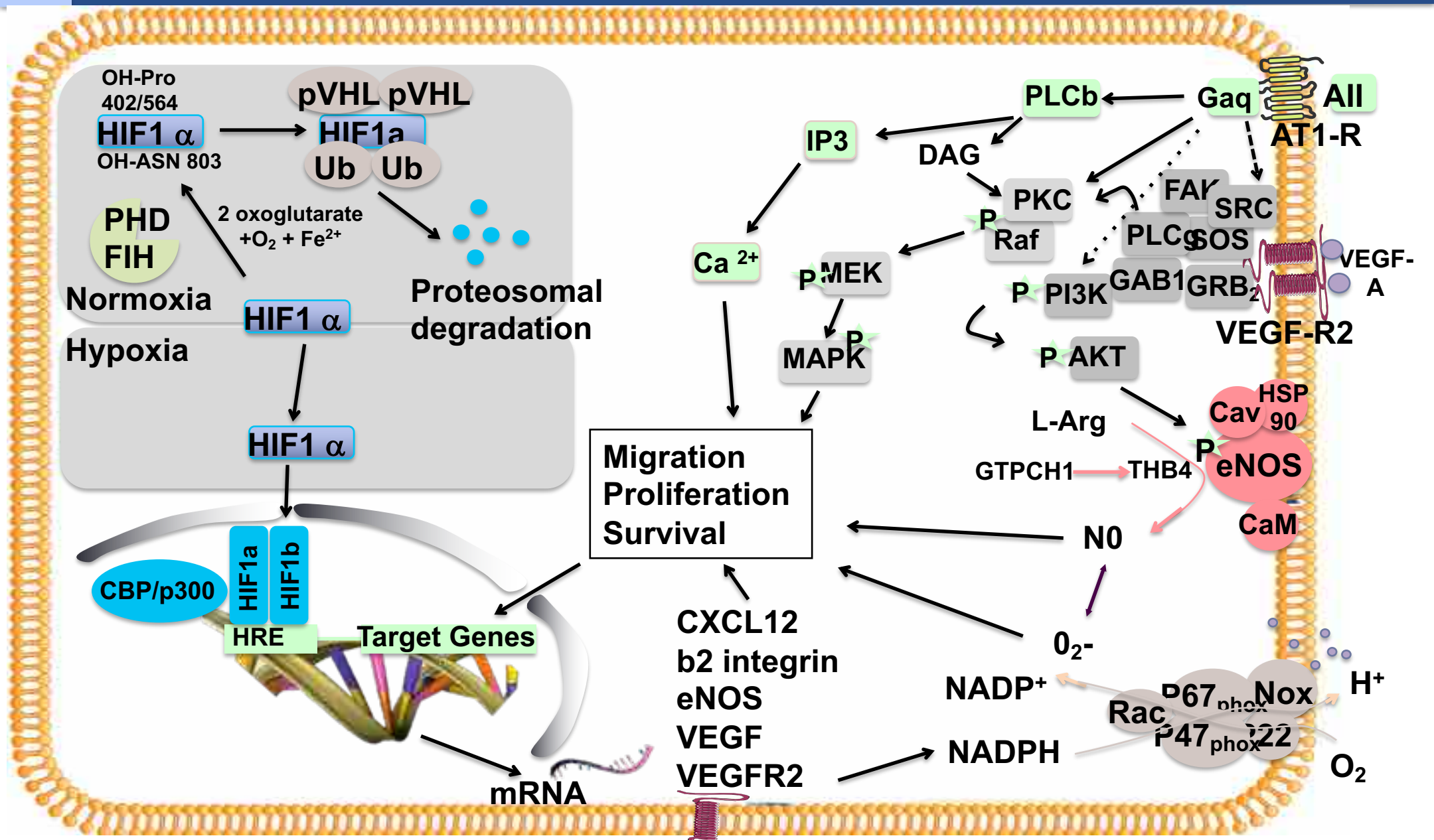
1- Modifications de l’arbre vasculaire et ischémie tissulaire



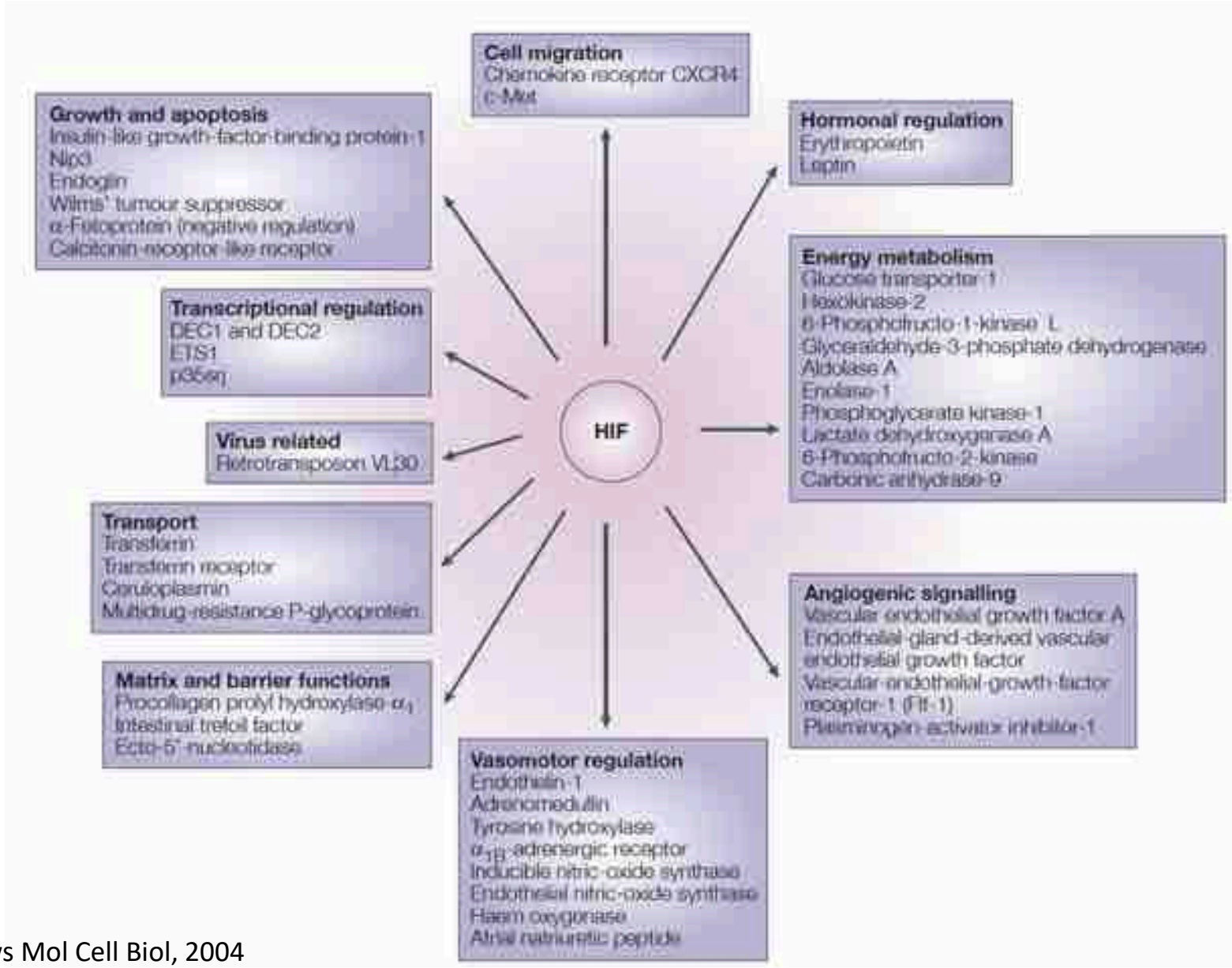
2- Mécanismes moléculaires et cellulaires



2-a La voie dépendante de HIF (Hypoxia inducible factor)

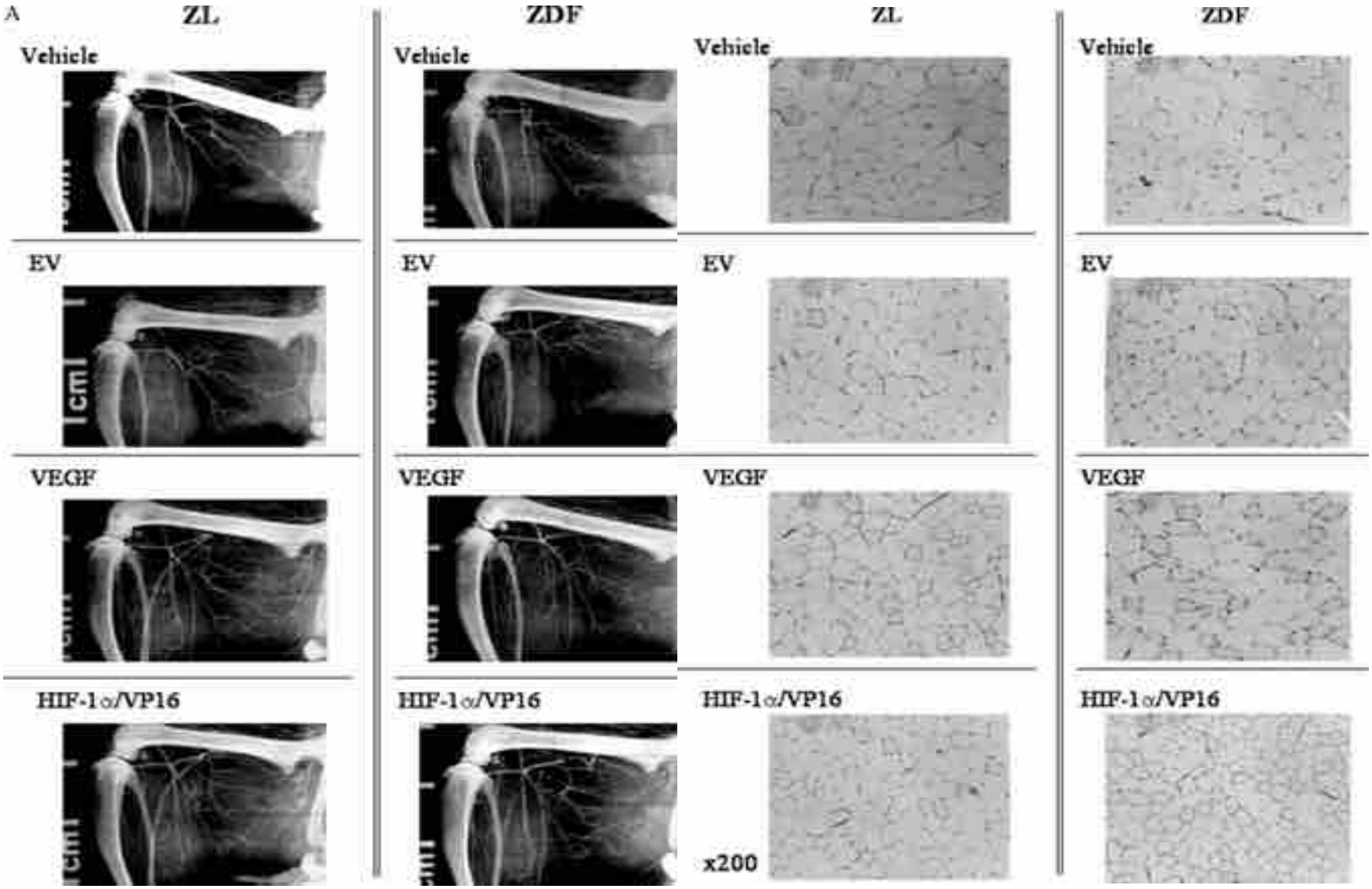


Les différentes cibles de HIF



Schofield C, Nat Reviews Mol Cell Biol, 2004

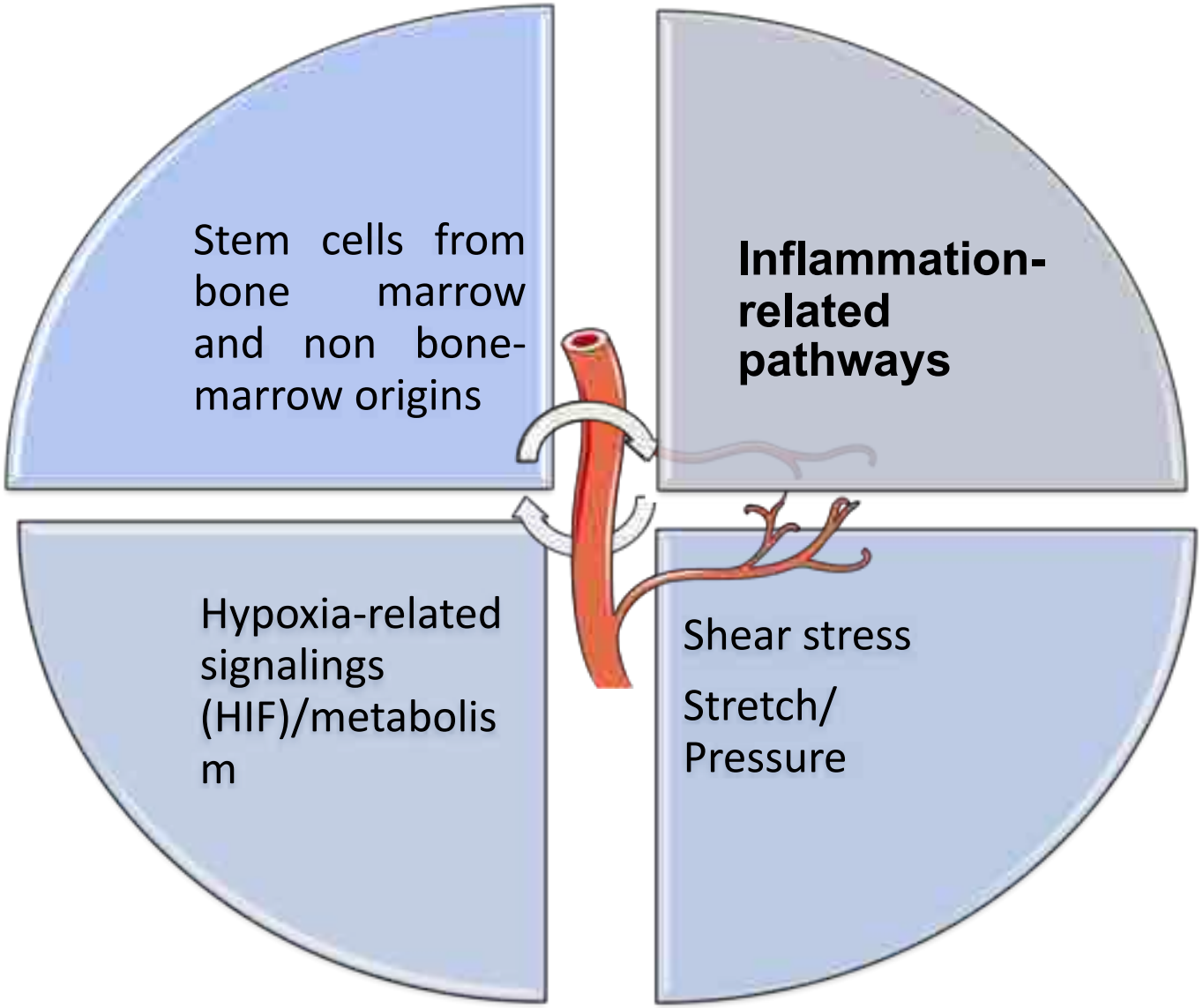
La surexpression de HIF1alpha active la revascularisation post-ischémique



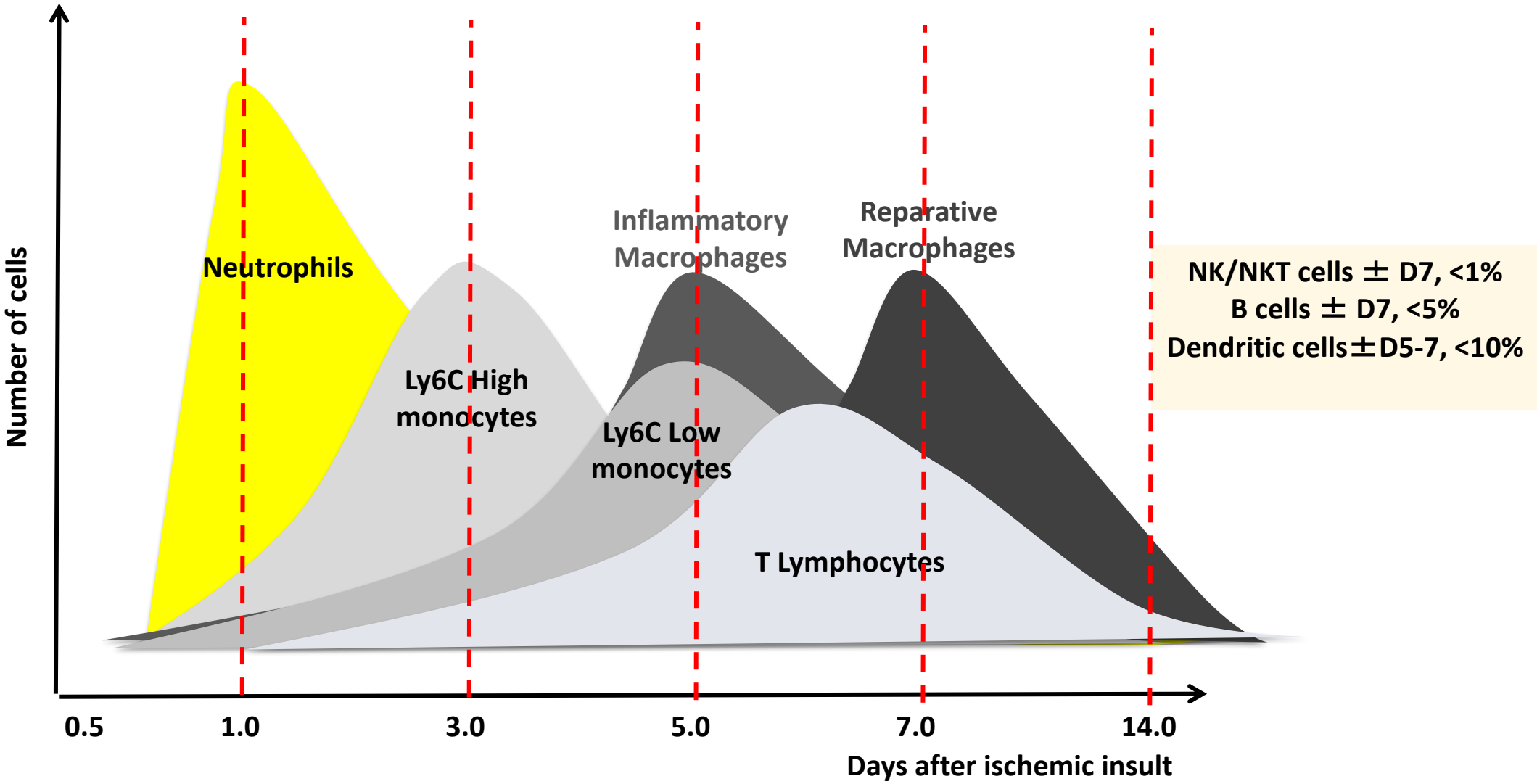
The HIF-1α/VP16 hybrid was constructed by truncating the transactivation and oxygen-dependent degradation domains of HIF-1α and then joining the HSV VP16 transactivation domain fragment downstream, to yield a normoxically stable, constitutively active form of HIF-1α

Kajiwara H, J Gene Med, 2009

2-b La voie dépendante de l'inflammation

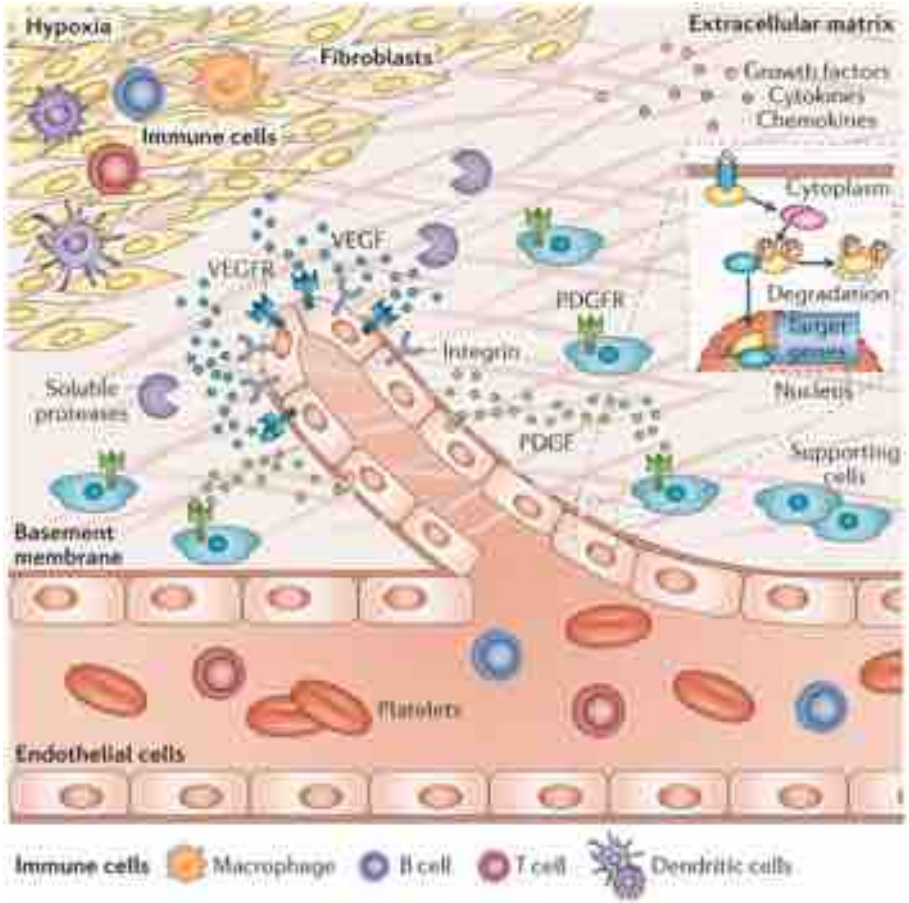


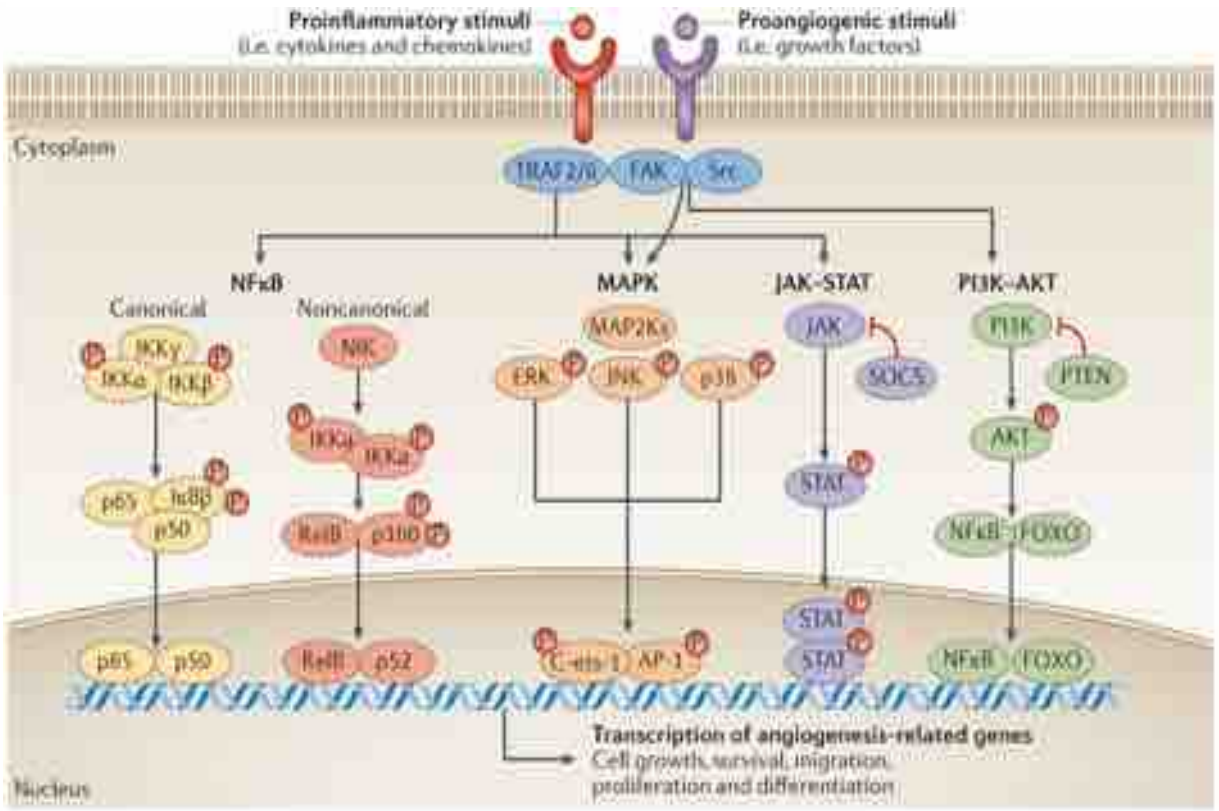
Infiltrat inflammatoire dans le tissu ischémique



Adapted from Silvestre JS et al, Physiol Rev, 2013

Inflammation et angiogenèse

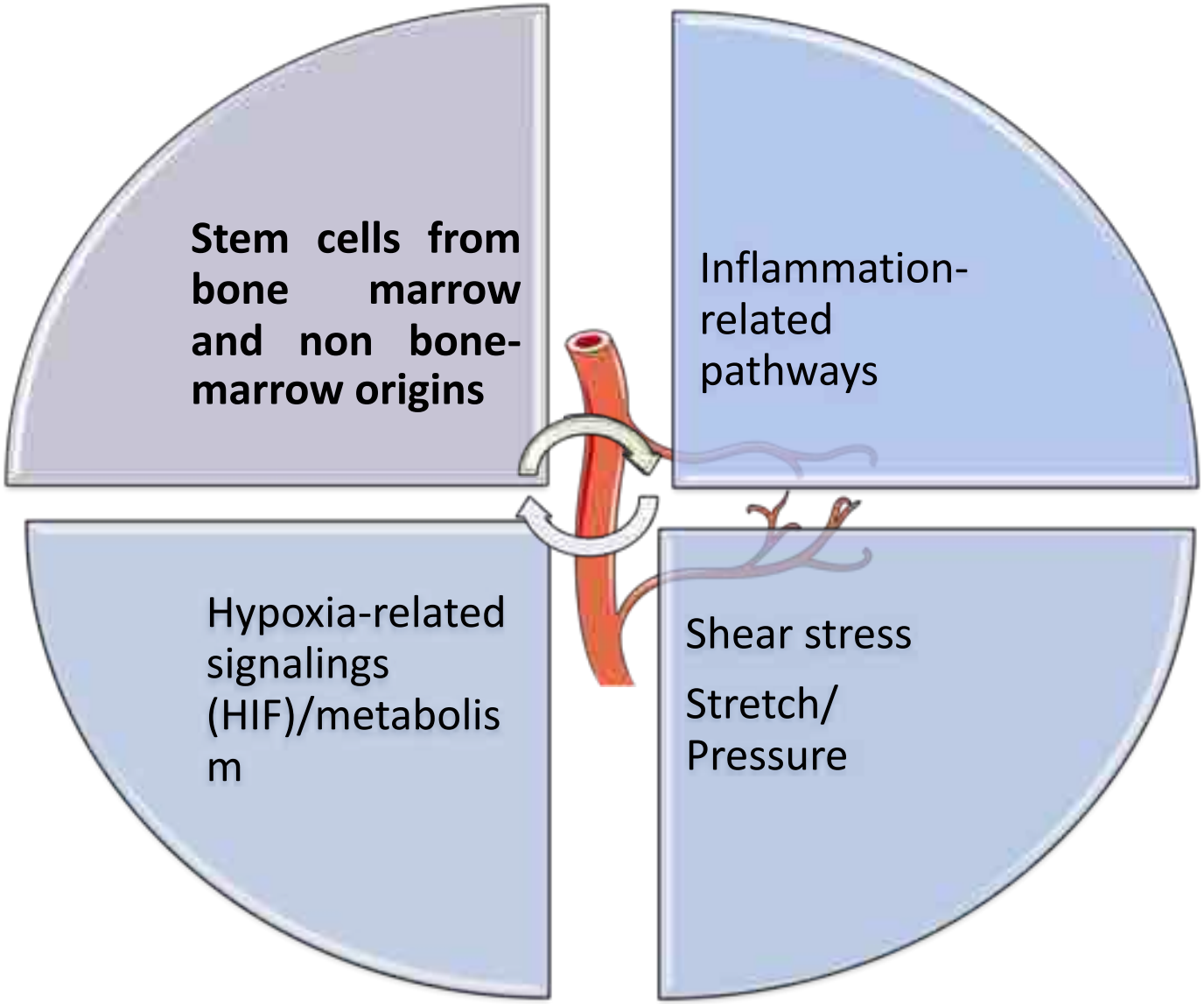




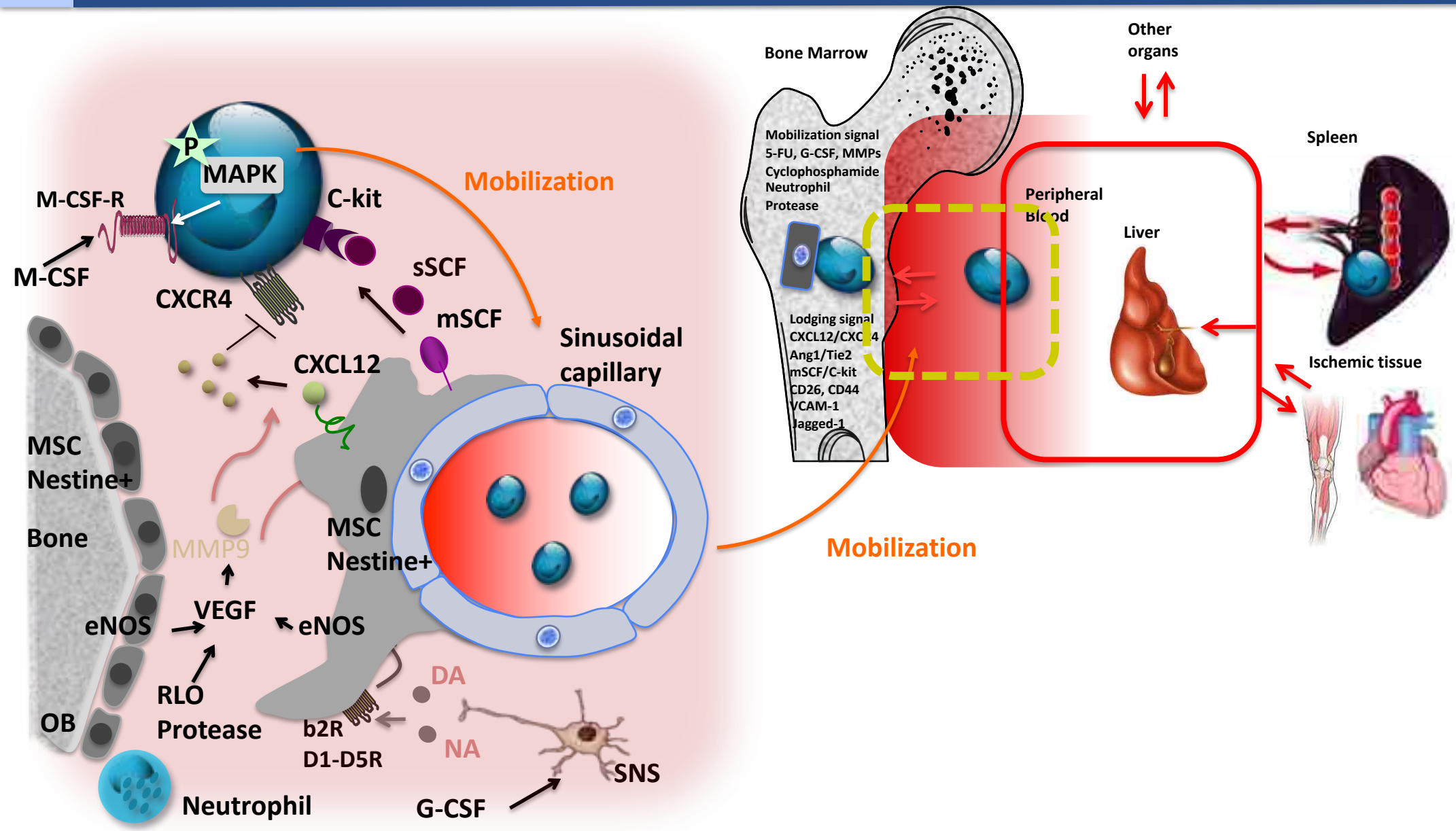
Phagocytose, Libération cytokines & facteurs de croissance
Protéolyse matricielle
Survie/Apoptose cellules résidentes

Tas, SW et al, Nat. Rev. Rheumatol., 2015

2-c La voie dépendante des cellules souches

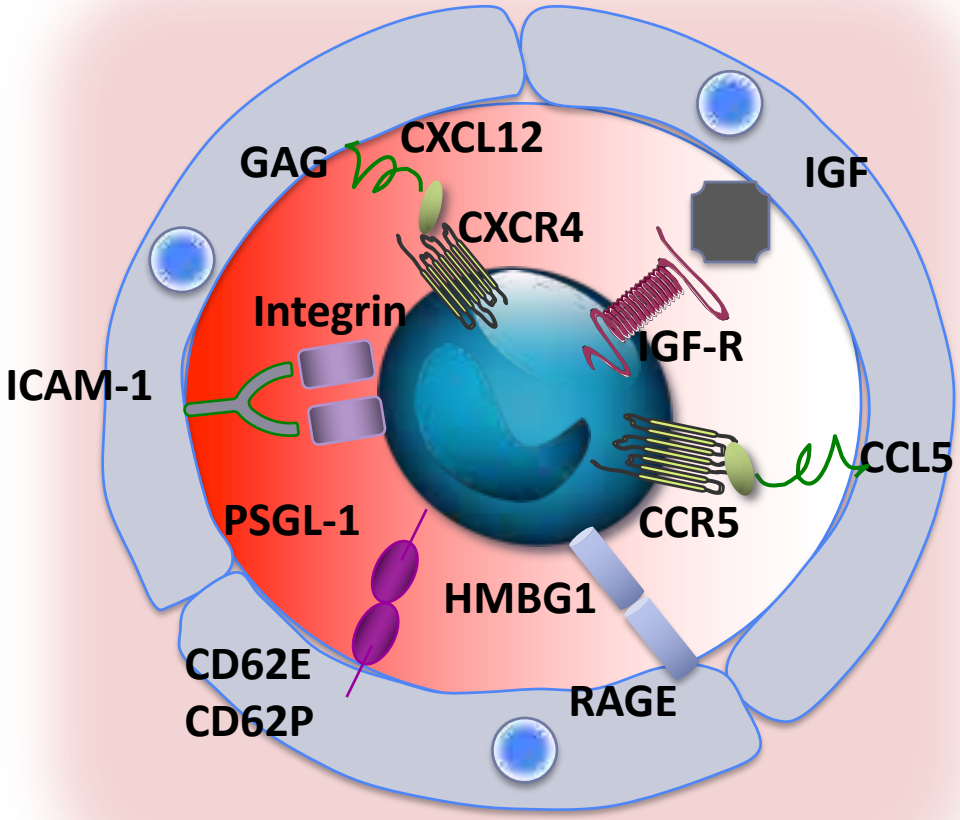


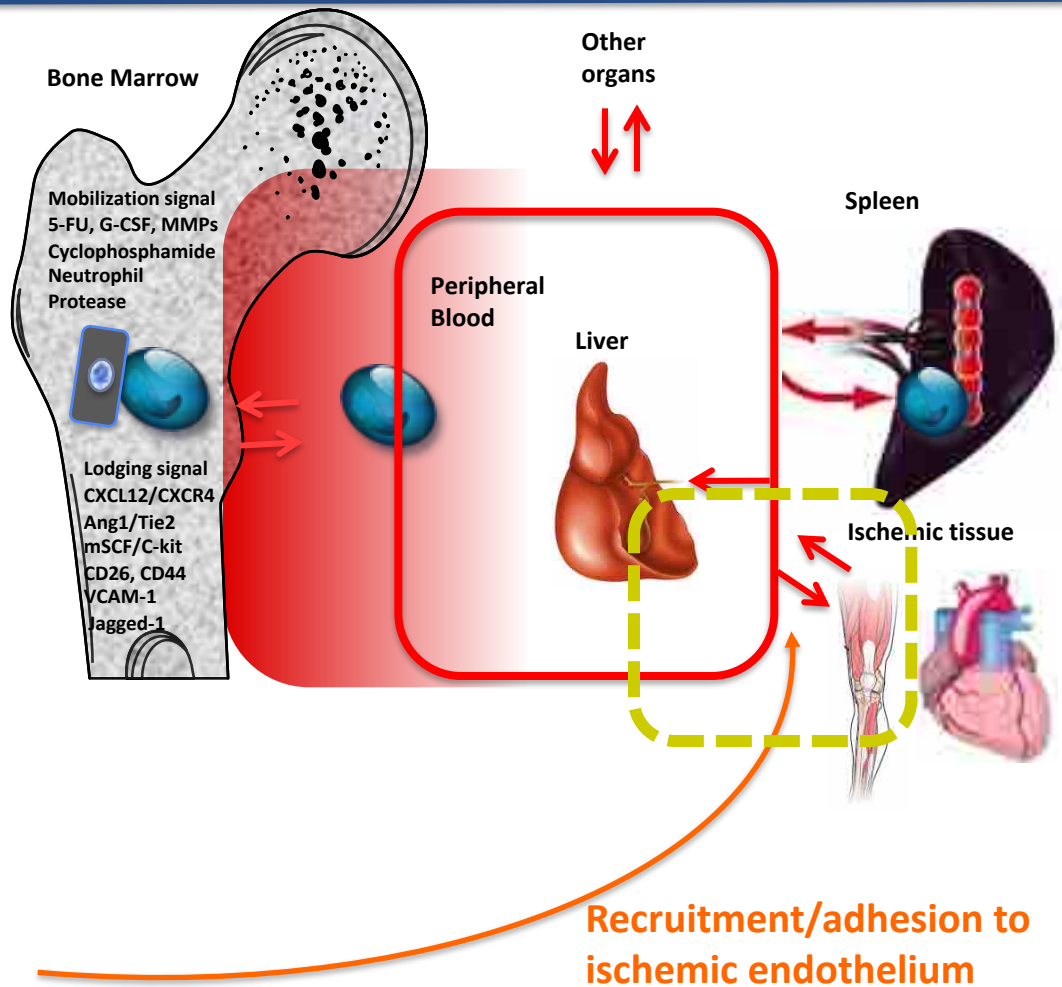
Mobilisation des cellules souches médullaires



Recrutement des cellules souches médullaires

Recruitment/adhesion to ischemic endothelium





Cellules souches/progénitrices d'origine médullaire

Bone marrow

Total or MNC,

MSC (CD34-, CD45-, CD19-, CD11a-, CD90+, CD105+, CD73+)

HSC (CD34+, CD117+, CD133+, Lin-),

Angiogenic cells (CD34+, CD133+, CXCR4+ …),

Side population (CD34-, CD117+, Sca-1+, Hoechst-)

Monocytes (CD14+, CD45+, CXCR2+,CD34-,CD133-, CD144-)

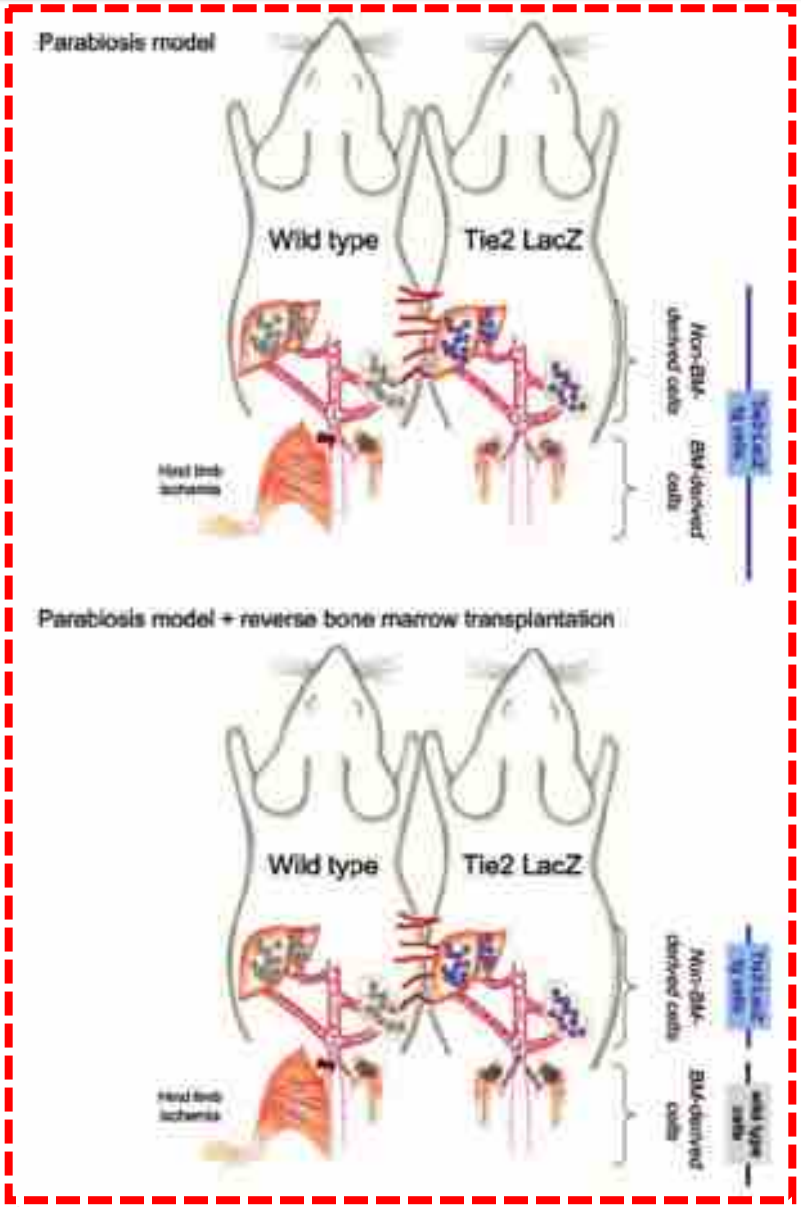
Blood

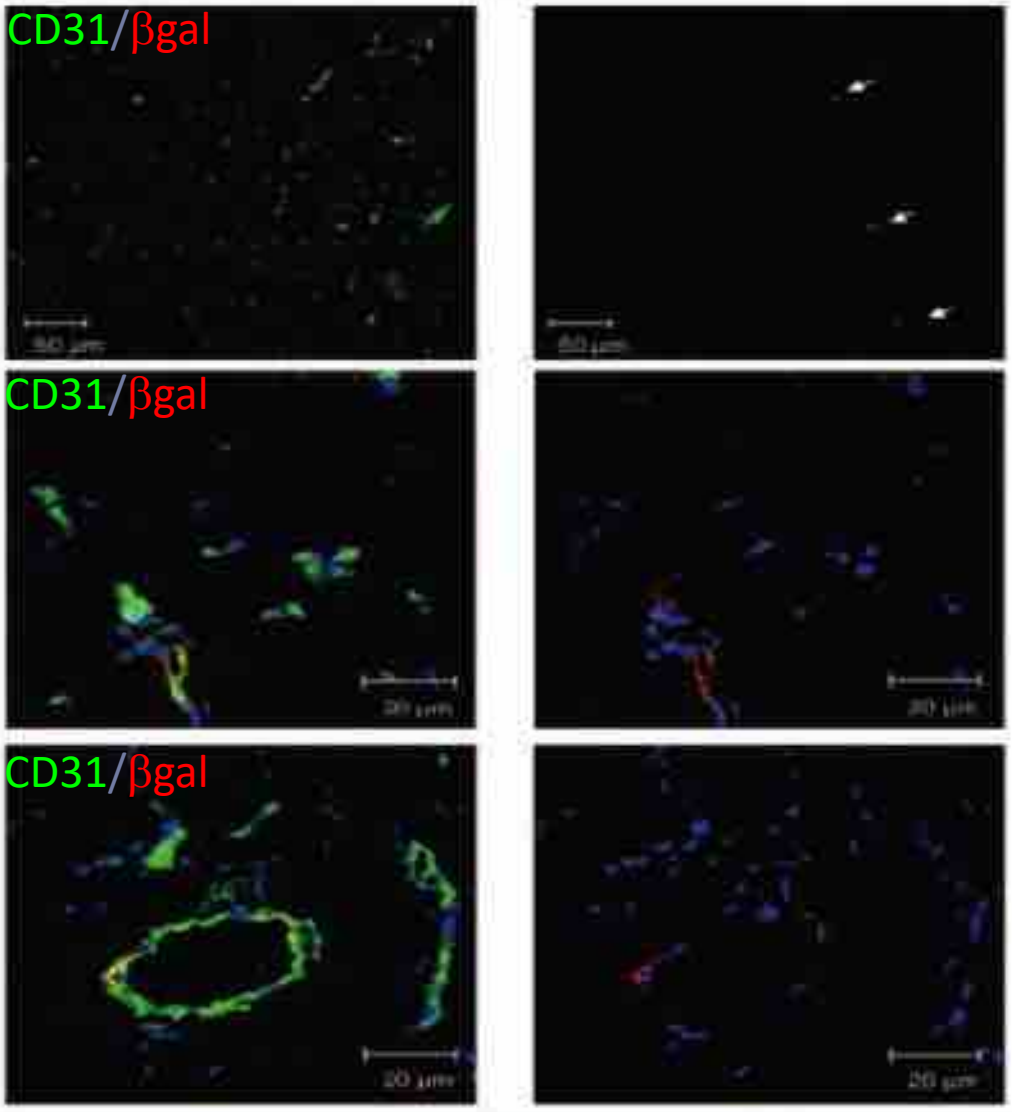
PB-derived MNC,

Monocytes (CD14+, CD45+, CXCR2+, CXCR3+ CD34-,CD133-,CD144-)

Angiogenic cells (early EPC, CXCR4+, CD133+, CD34+…)

Cellules souches/progénitrices d'origine extra-médullaire





Classic: 100% CD45-/ckit+

Reverse: 70% CD45-/ckit+

Aicher et al, Circ Res, 2007

Cellules souches/progénitrices adultes

Bone marrow

Total or MNC,

MSC (CD34-, CD45-, CD19-, CD11a-, CD90+, CD105+, CD73+)

HSC (CD34+, CD117+, CD133+, Lin-),

Angiogenic cells (CD34+, CD133+, CXCR4+ …),

Side population (CD34-, CD117+, Sca-1+, Hoechst-)

Monocytes (CD14+, CD45+, CXCR2+,CD34-,CD133-, CD144-)

Blood

PB-derived MNC,

Monocytes (CD14+, CD45+, CXCR2+, CXCR3+ CD34-,CD133-,CD144-)

Angiogenic cells (early EPC, CXCR4+, CD133+, CD34+…)

CB-derived MNC, CB-derived EPC (CD34+, CD133+, VEGFR2+, eNOS, CD144+), CB-derived SMPC (a-smooth muscle actin, myosin heavy chain, CX3CR1+)

Tissues

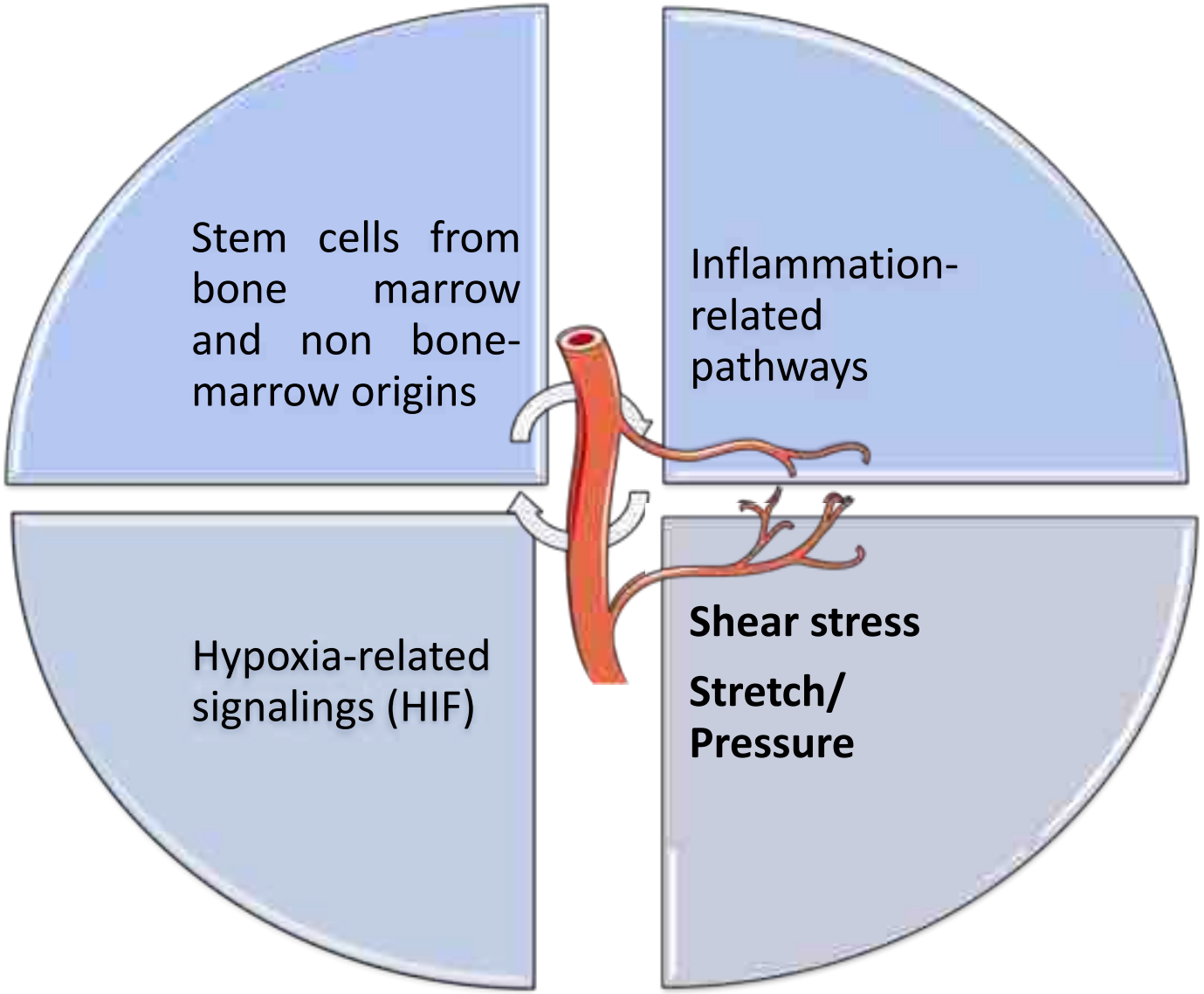
Heart (CD117+, Sca-1+, CD34+, Lin-, cardiosphere),

Vessel wall (CD34-,c-kit+, Sca-1+, Hoechst-),

Adipose tissue (SVF: CD34+, CD45low, CD14low, CD13, CD31+; ADSC: CD34+, CD31-, CD45-, CD105+),

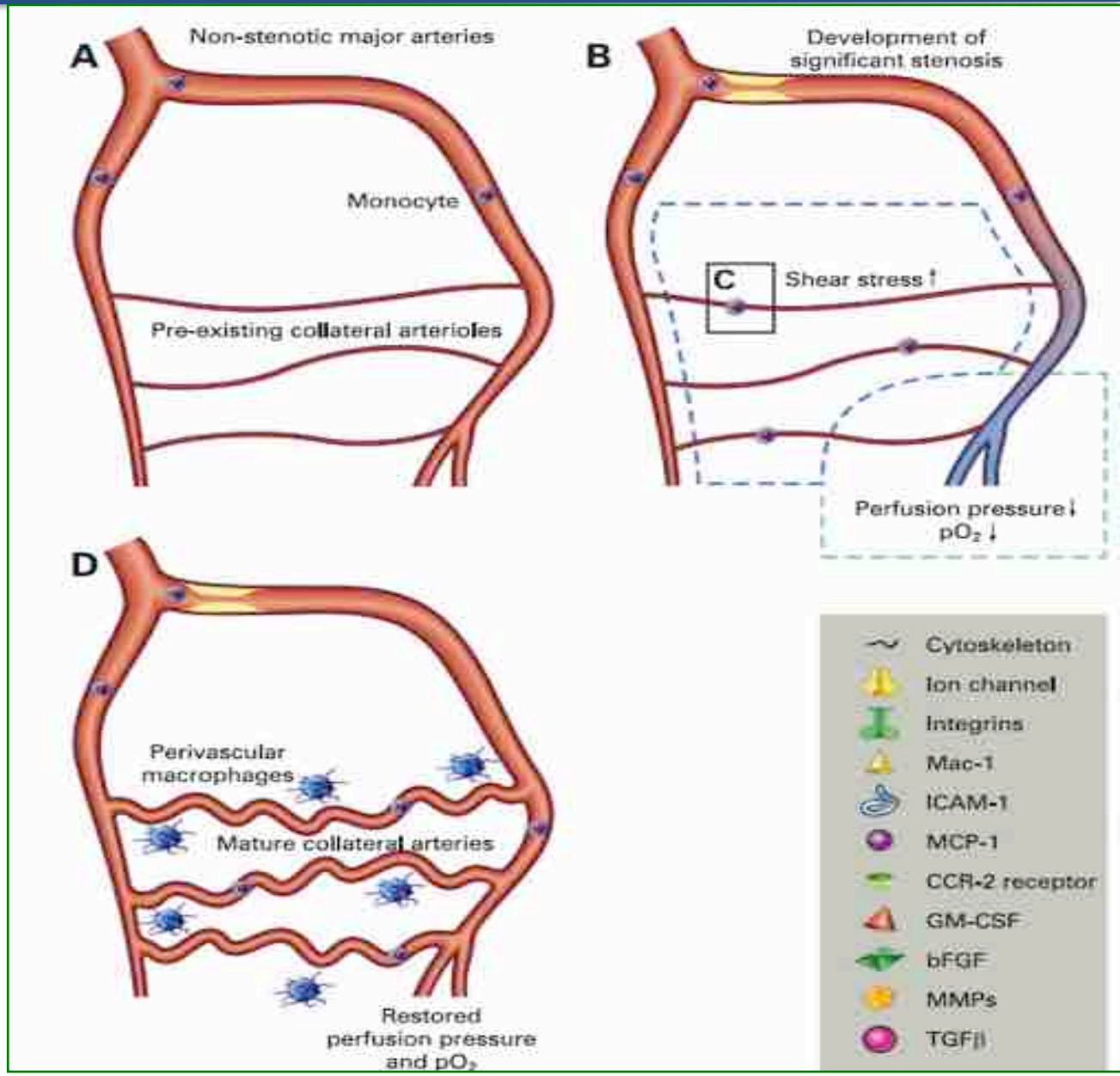
Skeletal muscle (CD34-,CD117+, Sca-1+, Hoechst-)

2-d La voie dépendante des facteurs hémodynamiques

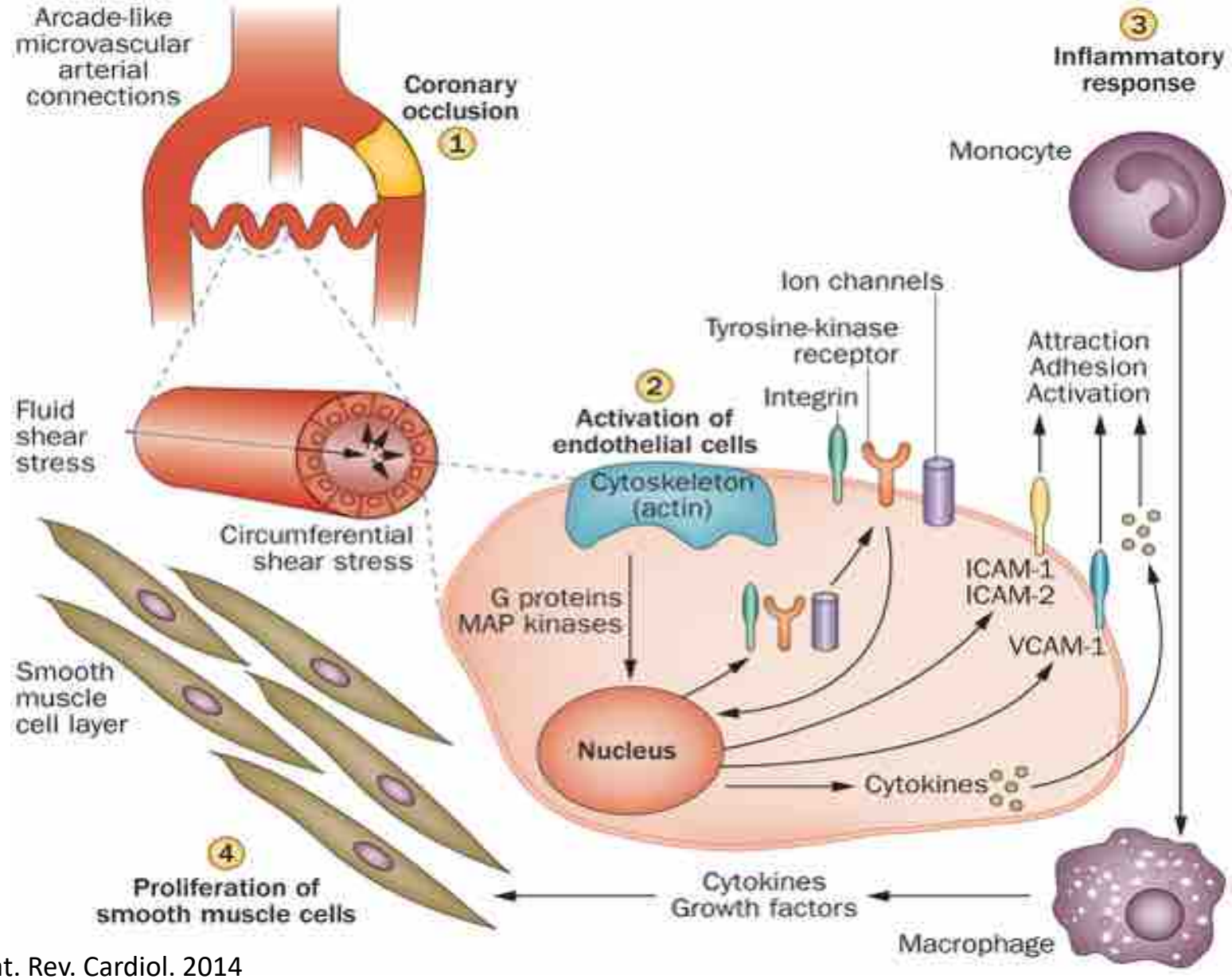


Forces hémodynamiques et collatéralisation

Modification de la structure du vaisseau (diamètre du vaisseau et épaisseur de la paroi artérielle) en réponse à une augmentation du débit sanguin dans l'artère collatérale

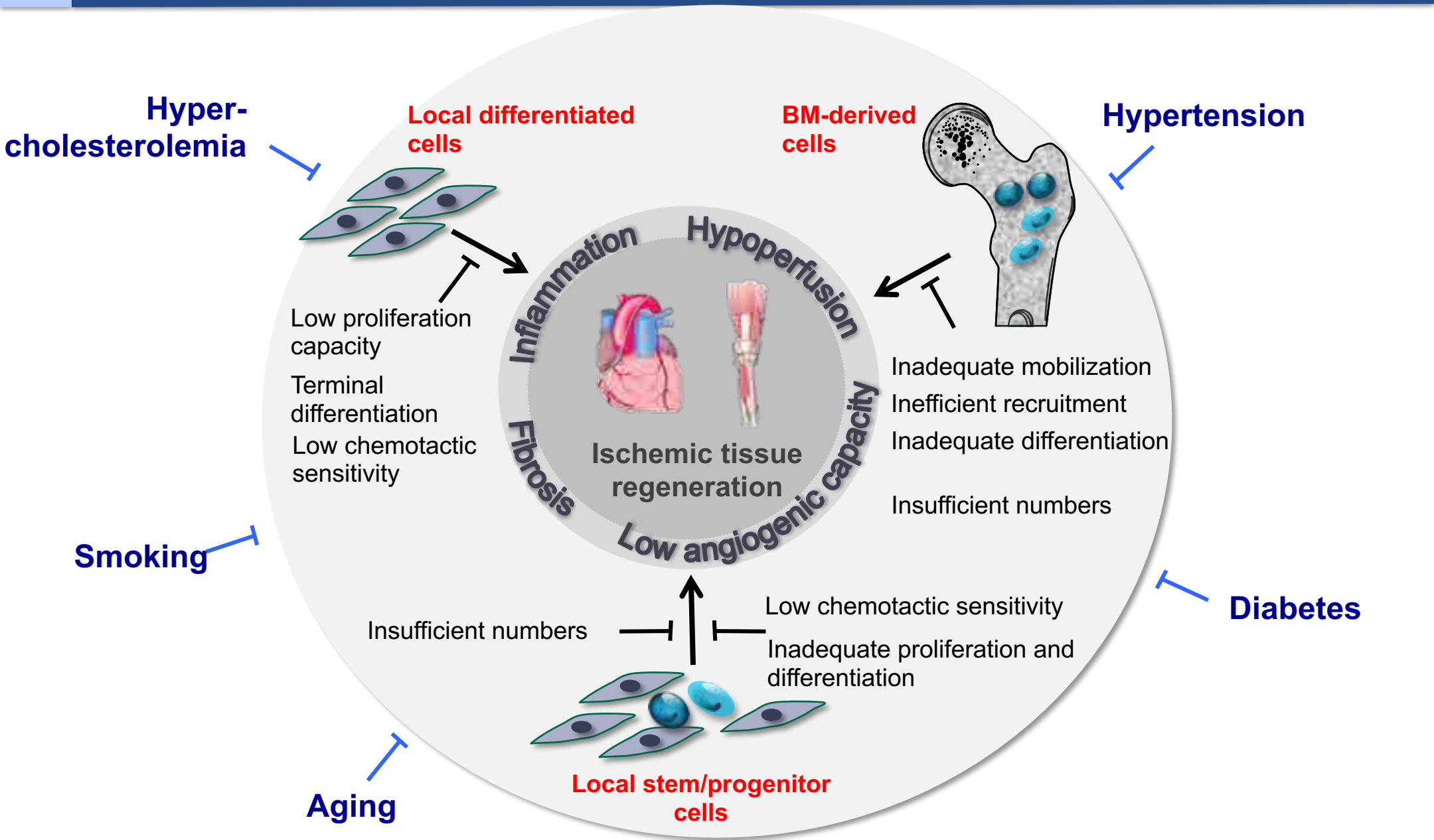


Les contraintes hémodynamiques



Zimarino, M. et al, Nat. Rev. Cardiol. 2014

3- Revascularisation thérapeutique

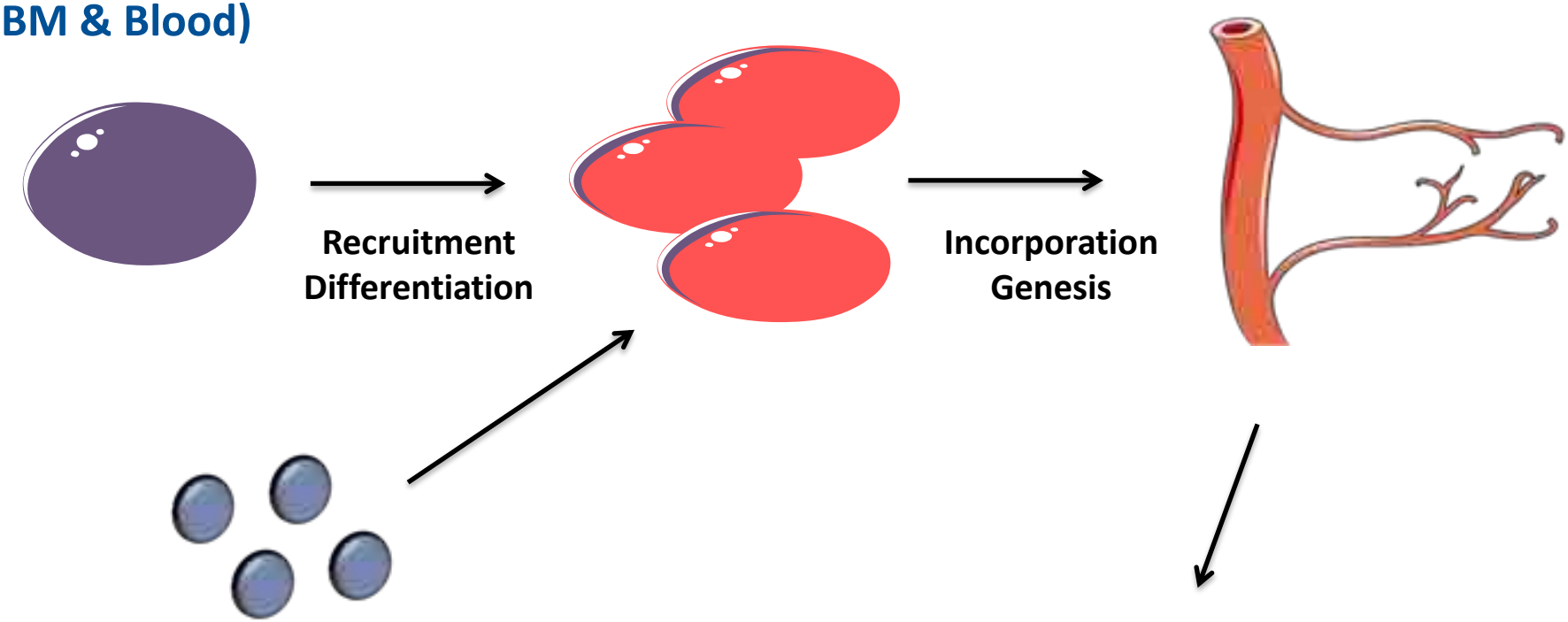


3- Revascularisation thérapeutique

Stem Cells (i.e EPC, MNC from BM & Blood)

Vascular cells (i.e. endothelial cells)

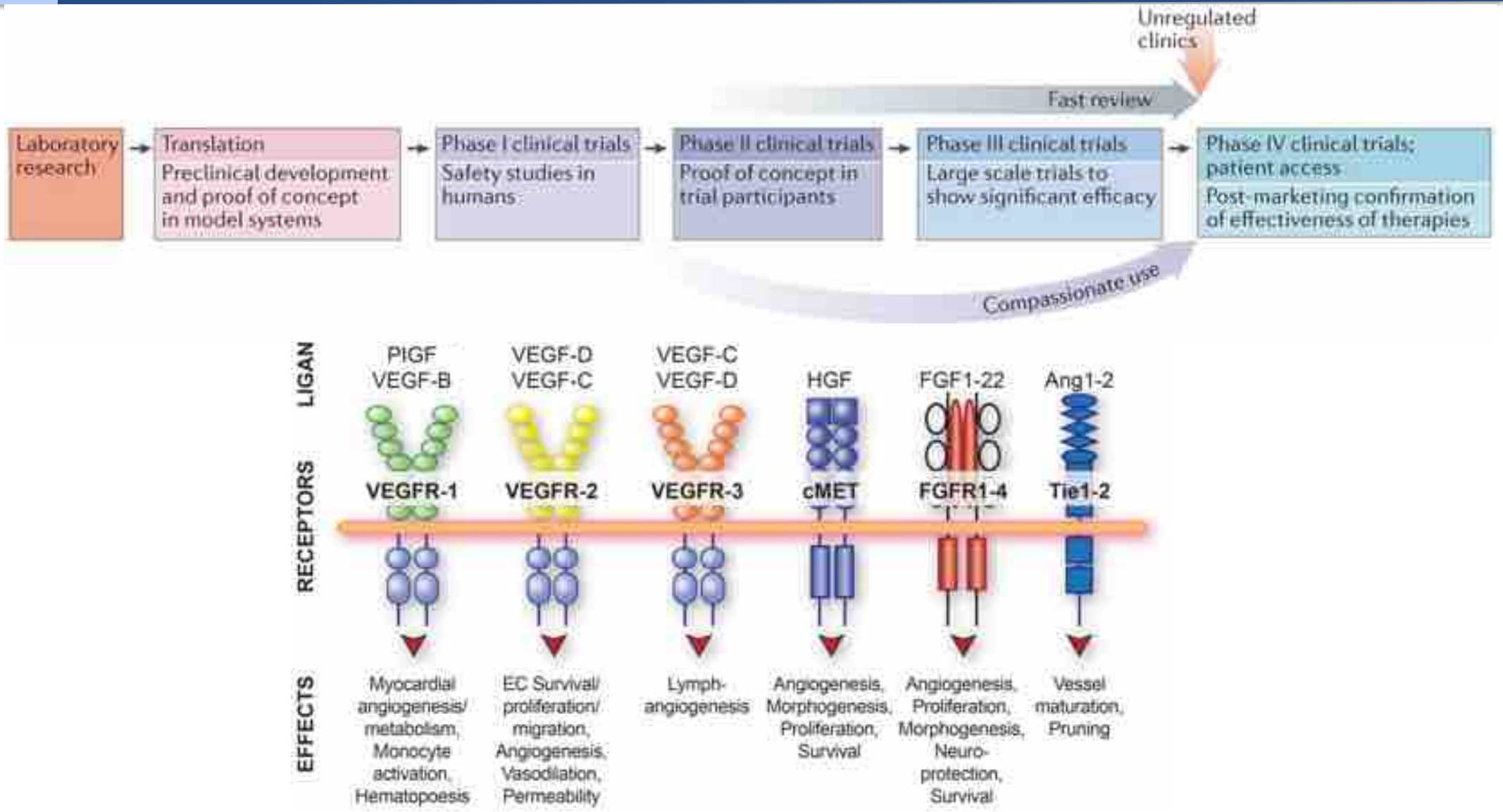
New vessels (i.e. capillary)



Pro-angiogenic agents (i.e GFs, Chemokines, Master gene)

Perfusion
Ischemic tissue homeostasis

Revascularisation thérapeutique: from bench to bedside



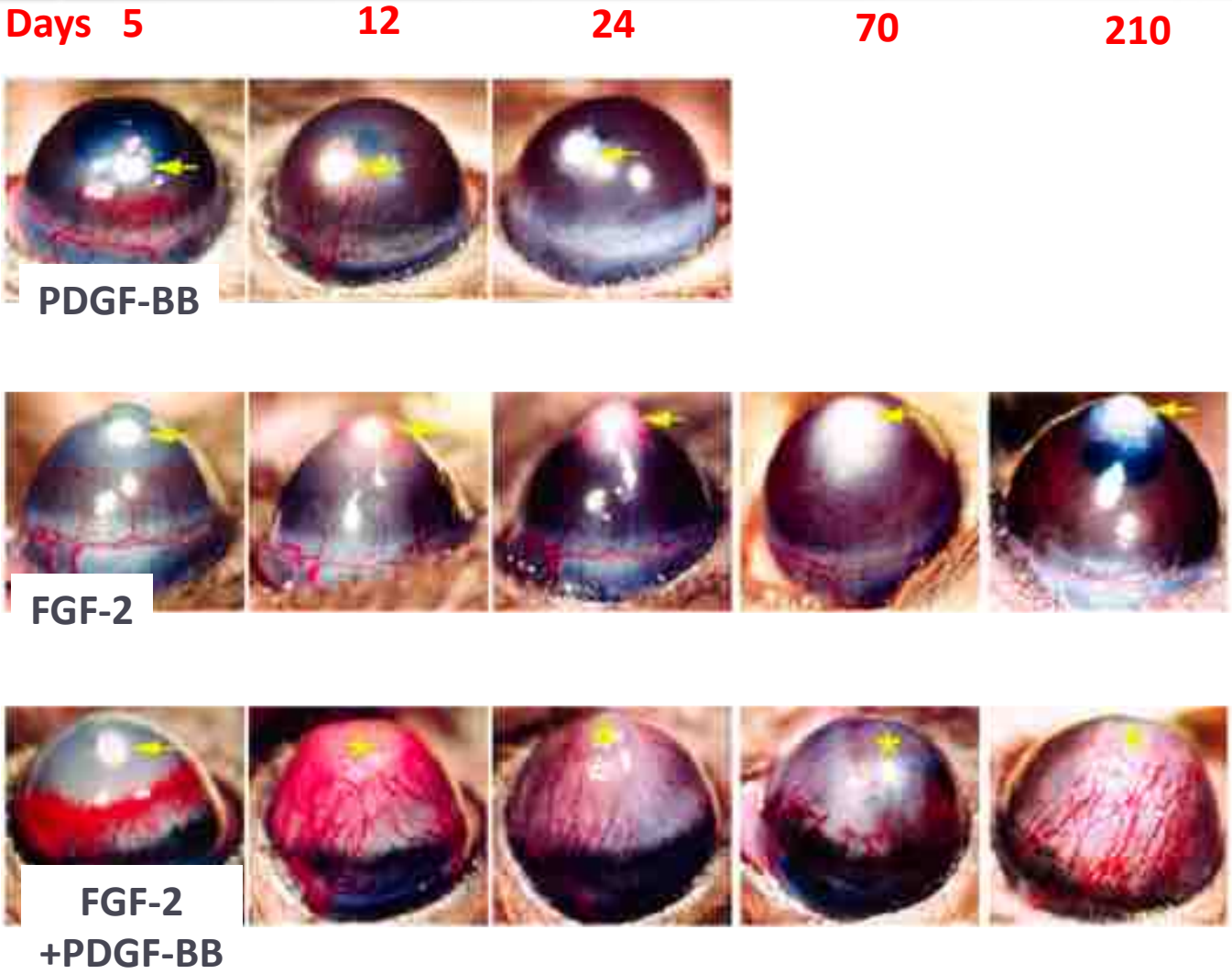
Yla-Herttuala SY et al, Eur Heart J, 2017

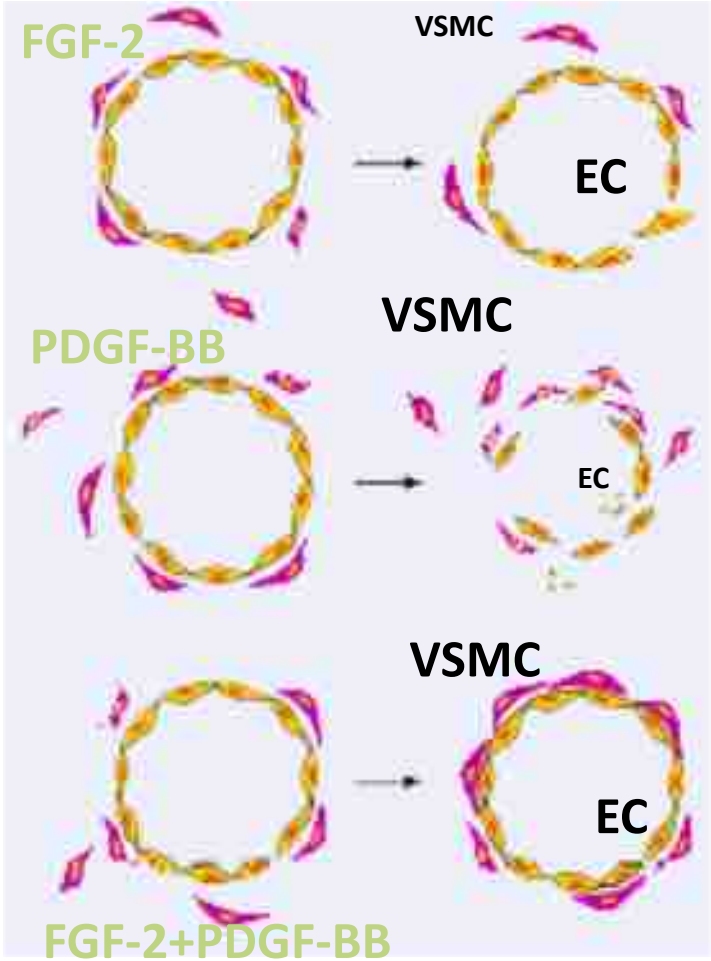
Trounson A, Nat Rev Mol Cell Biol, 2016

3-a Thérapie génique: facteurs de croissance vasculaire

Growth factor	Vectors	Site of injection	Clinical settings	Primary endpoint	References
VEGF	Recombinant protein	Intra-coronary+Intravenous	CHD	Negative	Henry et al. 2003
VEGF165	Adenovirus	Catheter-mediated	CHD	Positive	Hedman et al. 2003
VEGF165	Plasmid	Intramuscular	CLI	Negative	Kusumanto et al. 2006
VEGF165	Plasmid	Catheter-mediated	CHD	Negative	Kastrup et al. 2005
VEGF165	Plasmid	Catheter-mediated	CHD	Negative	Stewart et al. 2009
VEGF121	Adenovirus	Intramuscular	CLI	Negative	Rajagopalan et al. 2003
VEGF121	Adenovirus	Intramuscular	CHD	Negative	Stewart et al. 2006
VEGF121	Adenovirus	Intramuscular	CHD	Negative	Kastrup et al. 2011
VEGF121	Adenovirus	Intramuscular	CLI	Negative	Rajagopalan et al. 2003
FGF-2	Recombinant protein	Intra-coronary	CLI	Positive	Lederman et al. 2003
FGF-2	Recombinant protein	Intra-coronary	CHD	Negative	Simons et al. 2003
FGF-1	Plasmid	Intramuscular	CLI	Positive	Nikol et al. 2008
HGF	Plasmid	Intramuscular	CLI	Positive	Powell et al. 2008
HGF	Plasmid	Intramuscular	CLI	Positive	Shigematsu et al. 2010
HGF	Plasmid	Intramuscular	CLI	Positive	Powell et al. 2010
HGF	Plasmid	Intramuscular	CLI	Positive	Morishita et al. 2011
2 HGF isoforms	Plasmid	Intramuscular	CLI	Positive	Henry et al. 2011
Del-1	Plasmid and poloxamer	Intramuscular	CLI	Negative	Grossman et al. 2007

Amélioration de l'efficacité des thérapies géniques: bi-thérapie





Cao R et al, Nature Medicine, 2003

Amélioration de l'efficacité des thérapies géniques: bi-thérapie

Phase 2, double-blind trial in 52 CLI patients, safety and potential efficacy of intramuscular injections of low-dose (*n*=21) or high-dose (*n*=20) VM202 or placebo (*n*=11) in the affected limb (days 0, 14, 28 and 42)

√ Complete ulcer healing was significantly better in high-dose patients.

√ Clinically meaningful reductions (>50%) in ulcer area occurred in high-dose and low-dose groups

√ At 12 months, significant differences were seen in $TcPO_2$ between the high-dose and placebo groups

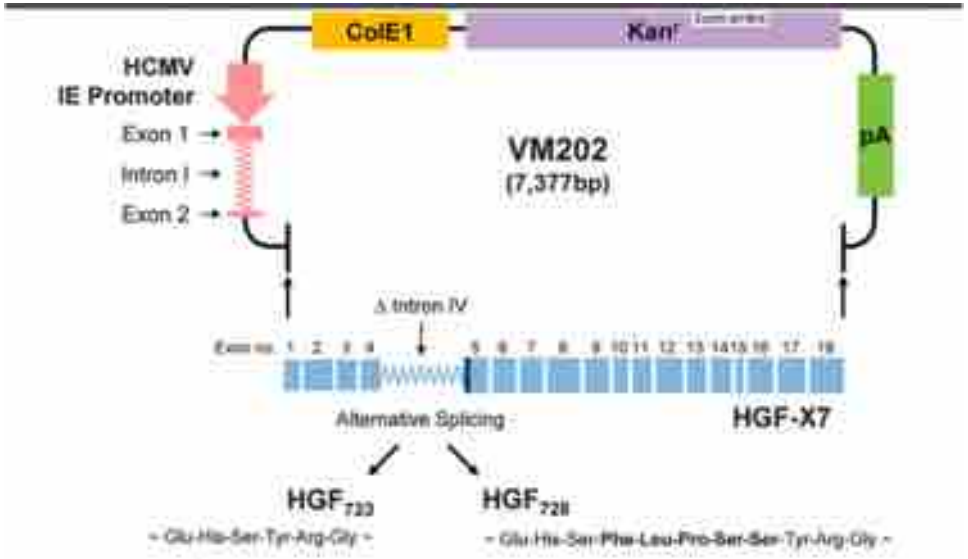
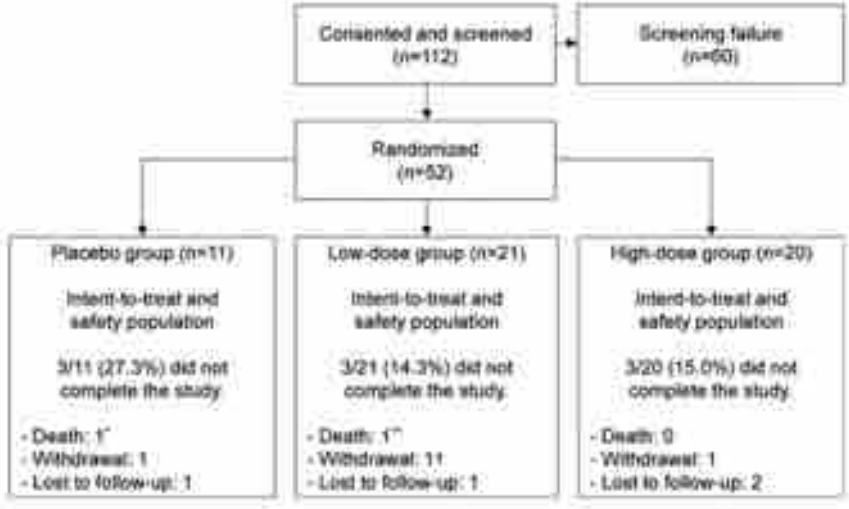


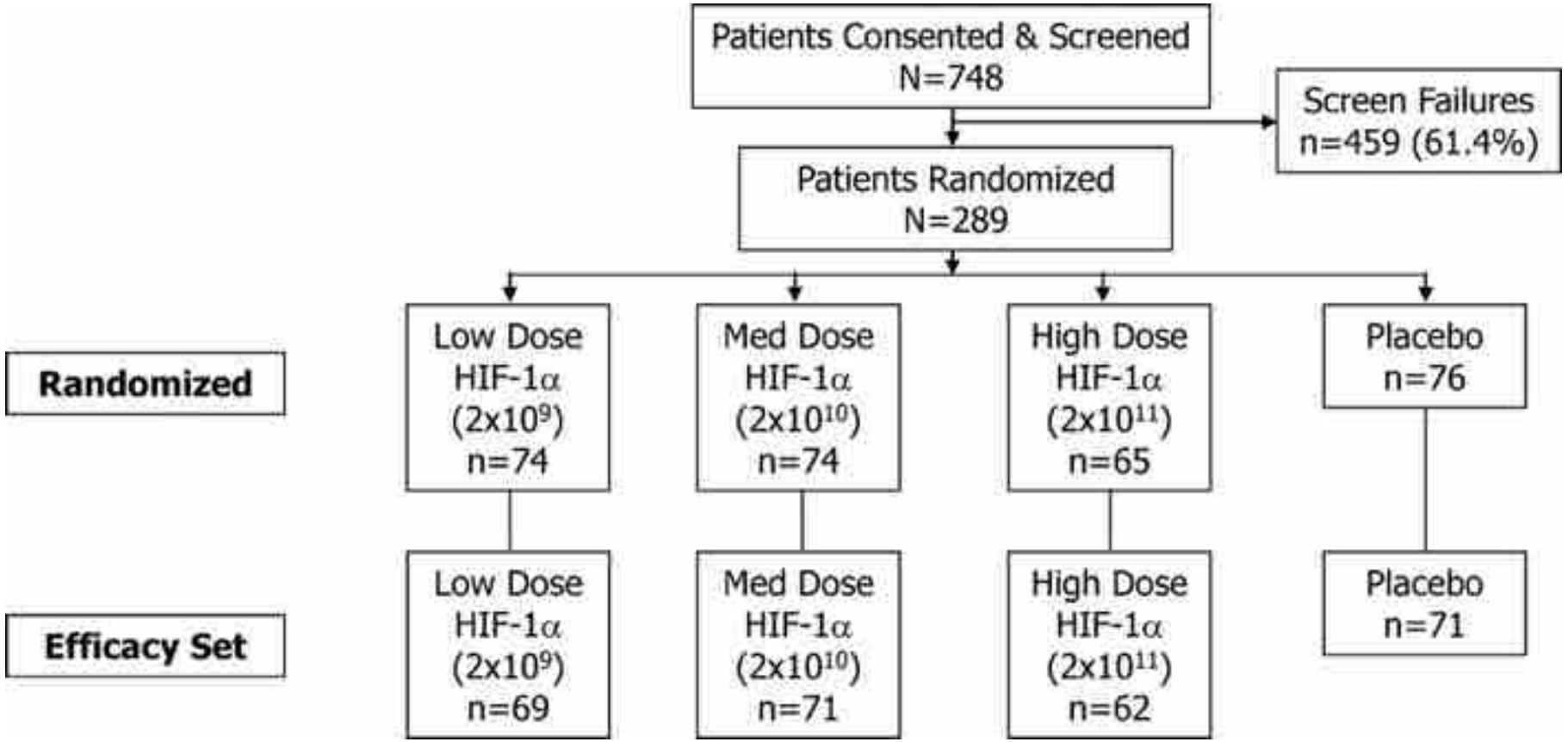
Figure 1. Schematic of the VM202 construct.



Kibbe MR, Gene Therapy, 2016

Amélioration de l'efficacité des thérapies géniques: Master gene?

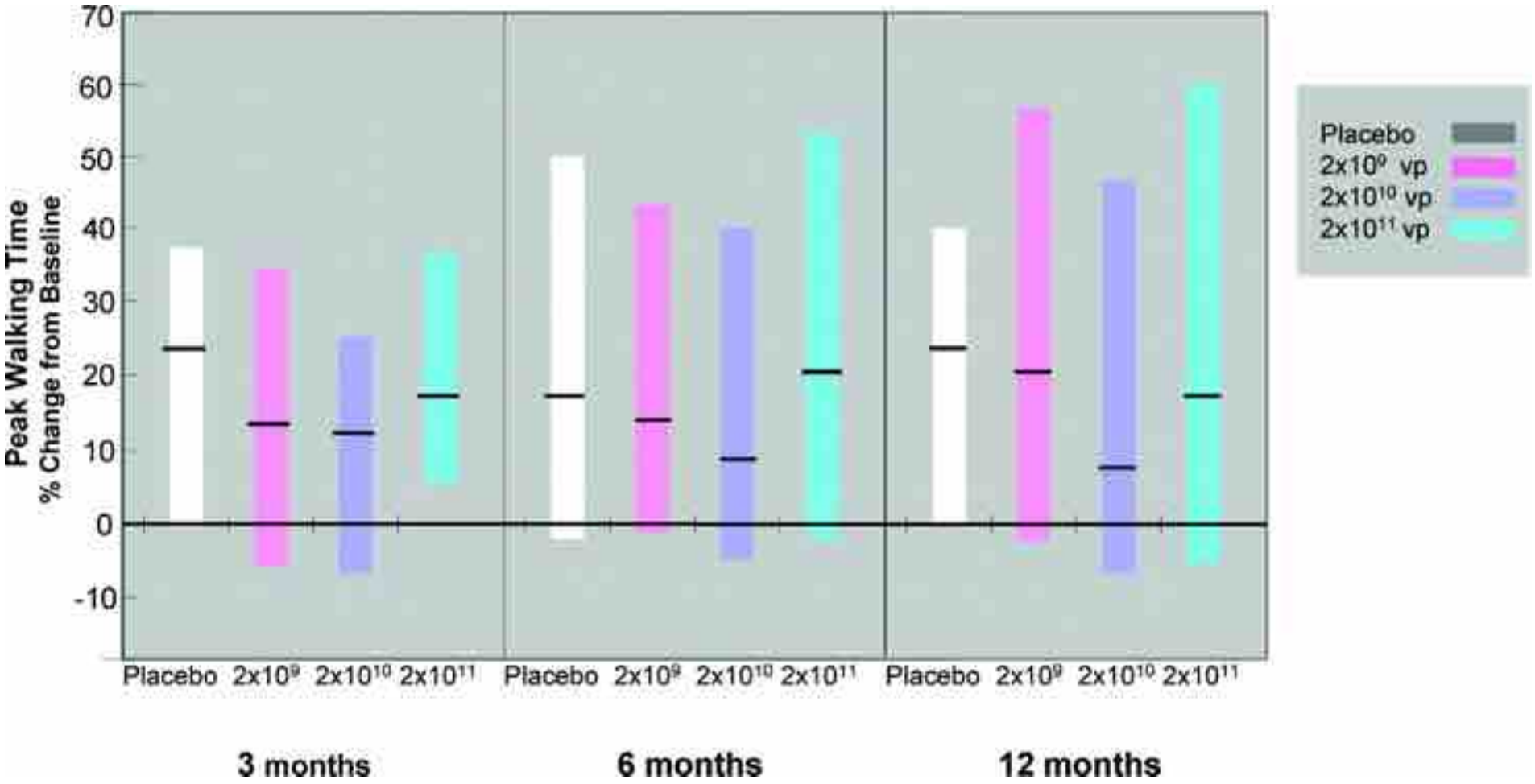
Two hundred eighty-nine patients with claudication were randomized in a double-blind manner to 1 of 3 doses of Ad2/HIF-1α/VP16 (2 × 10(9), 2 × 10(10), or 2 × 10(11) viral particles) or placebo, administered by 20 intramuscular injections to each leg.



Creager M A et al, Circulation, 2011

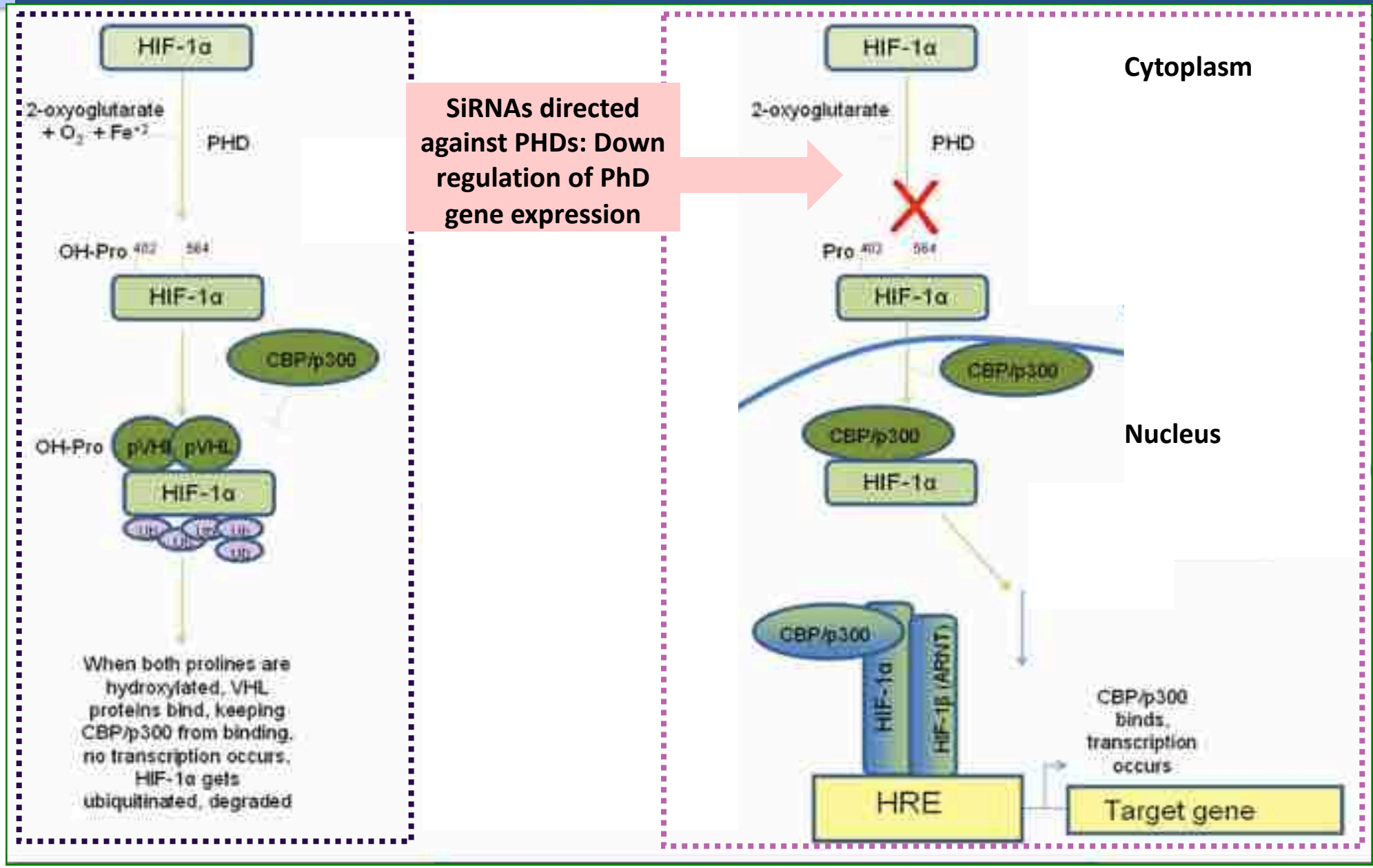
Amélioration de l'efficacité des thérapies géniques: Master gene?

The primary end point was the change in peak walking time from baseline to 6 months. The secondary end point was change in claudication onset time, and tertiary end points included changes in ankle-brachial index and quality-of-life assessments



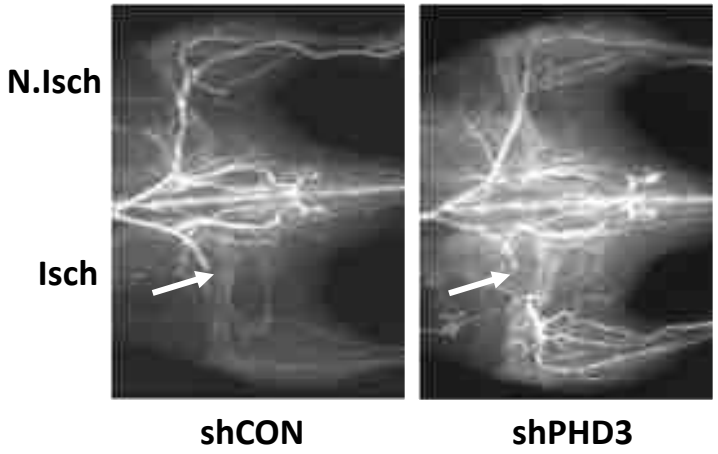
Creager M A et al, Circulation, 2011

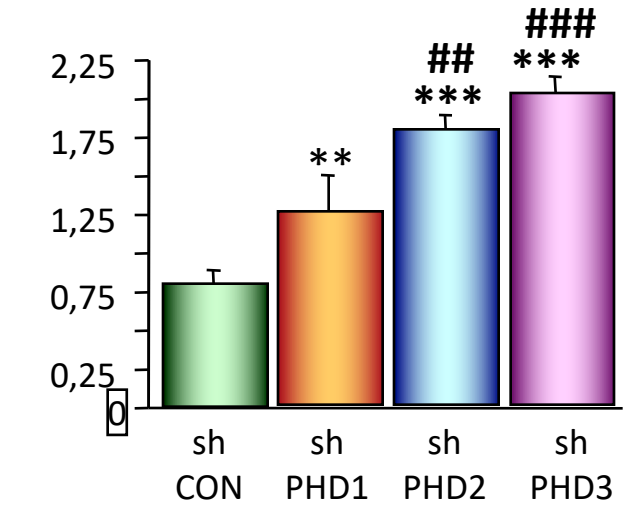
Amélioration de l'efficacité des thérapies géniques: Master gene?



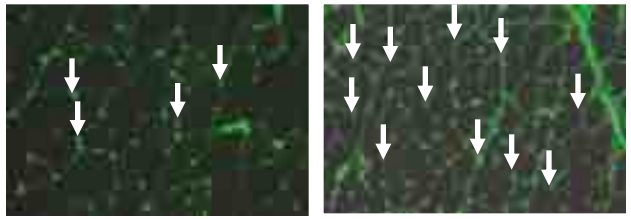
Amélioration de l'efficacité des thérapies géniques: Master gene?

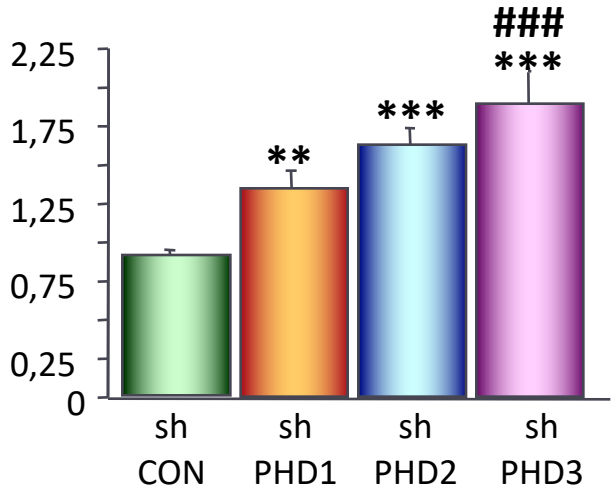
Angiographic score (Isch/N.Isch)



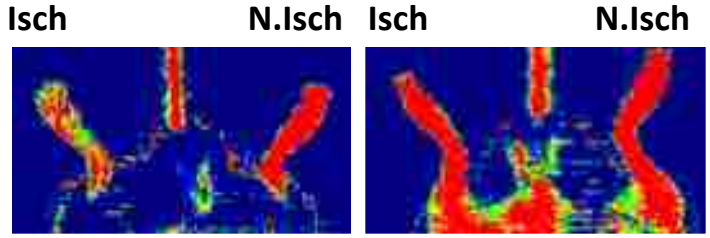


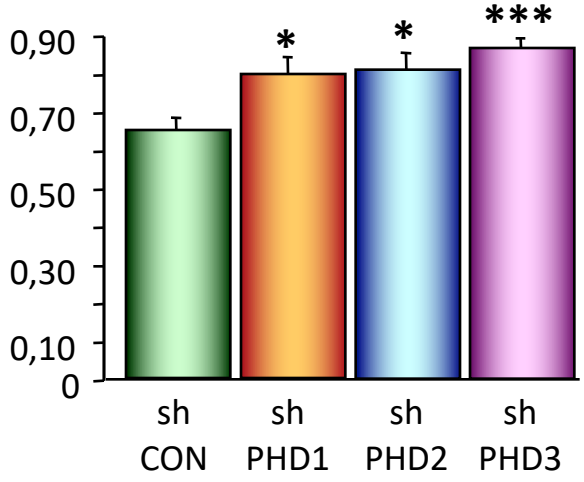
Capillary density (Isch/N.Isch)





Tissue perfusion (Isch/N.Isch)

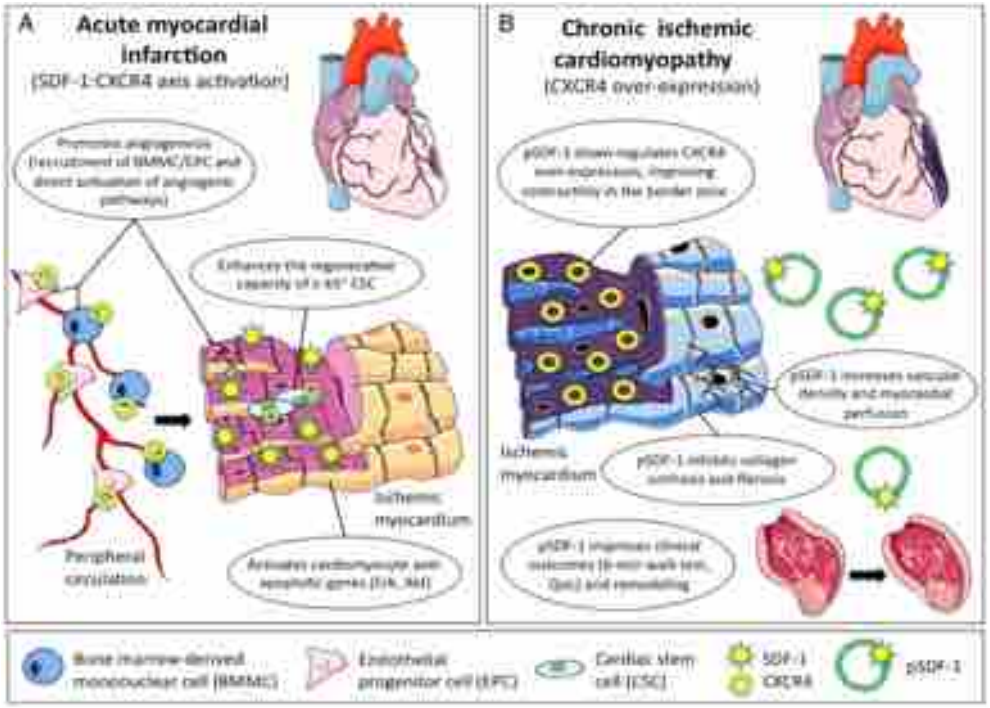




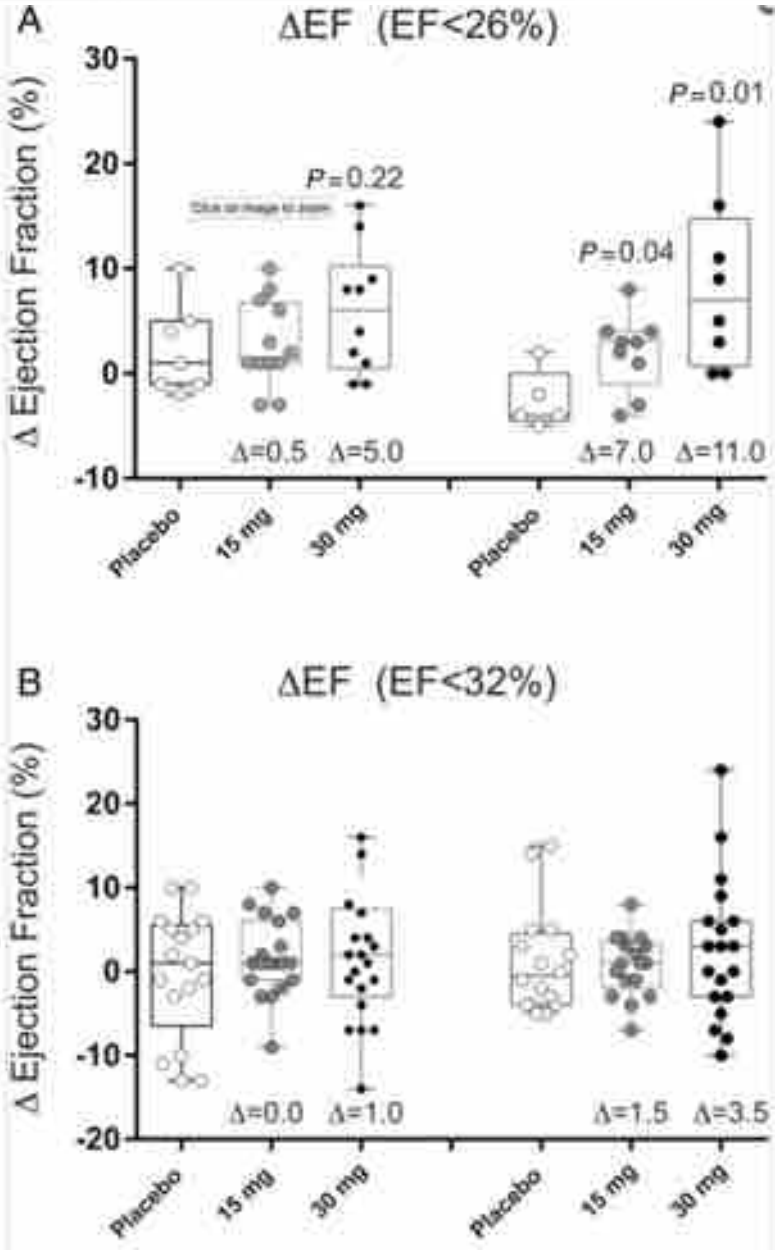
Loinard C et al, Circulation, 2009

Amélioration de l'efficacité des thérapies géniques: Master gene?

Ninety-three subjects with IHF on stable guideline-based medical therapy and left ventricular ejection fraction (LVEF) ≤40%, were randomized 1 : 1 : 1 to receive a single treatment of either a 15 or 30 mg dose of pSDF-1 or placebo via endomyocardial injections. Safety and efficacy parameters were assessed at 4 and 12 months after injection.



Chung ES et al, Eur Heart J, 2015



Thérapies géniques - essais cliniques en cours

Table I Currently on-going or planned gene therapy trials in coronary artery disease and peripheral arterial disease

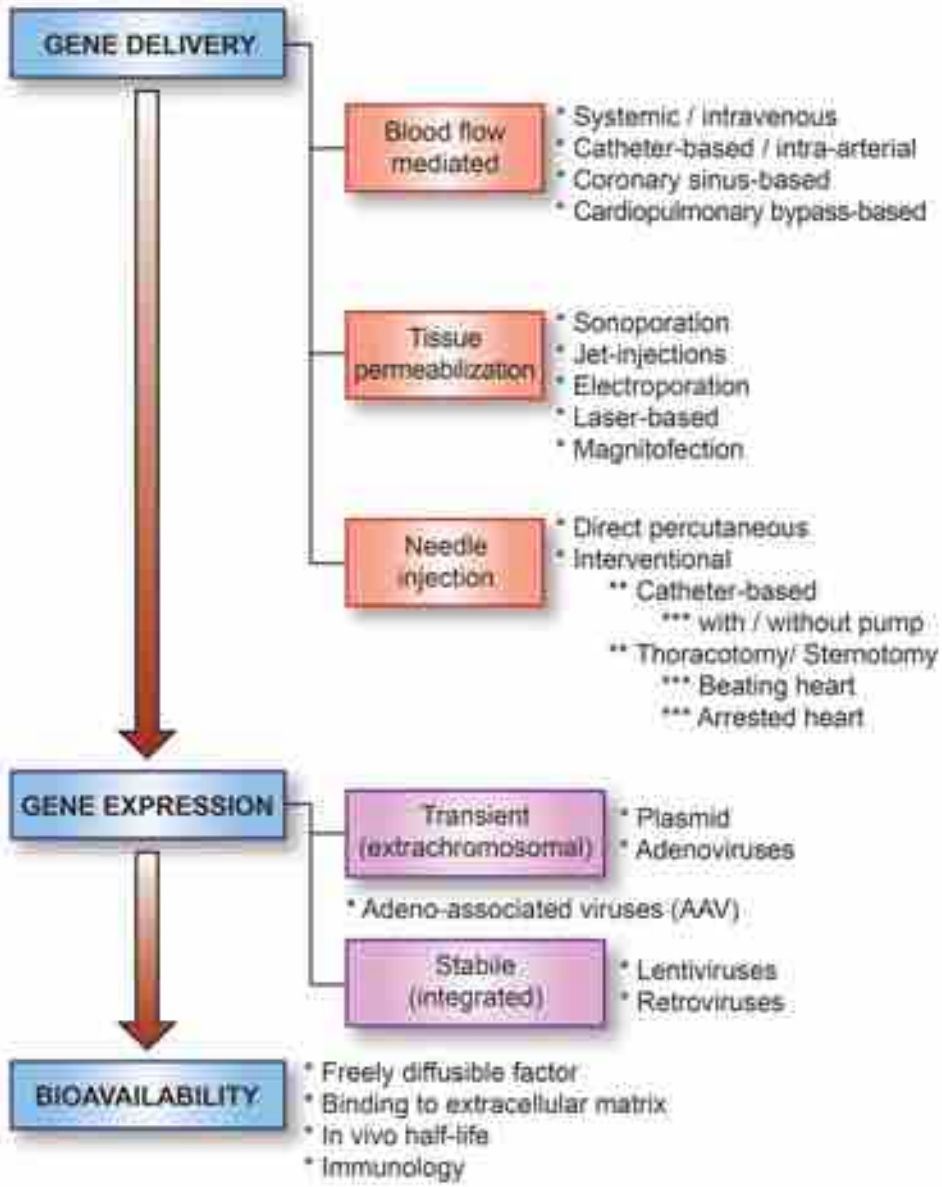
Trial name or ID	Disease	GP	Vector	Delivery	Pat no	Novelty	Status
Trials aiming for physiological angiogenesis							
NCT01757223	CAD	VEGF-A116A	Ad	i.myo.(tct)	41	Expression of 3 different VEGF-A isoforms	Planned
NCT00956332	PAD	VEGF-A+Ang-1	RV	i.a.	28	Ang-1 should stabilize vessels induced by VEGF-A +RV used	Results pending
NCT00390767	PAD	VEGF-A+Ang-1	RV	i.a.	12	Ang-1 should stabilize vessels induced by VEGF-A +RV used	Results pending
Trials using therapeutic vascular growth in combination with other treatments							
KAT-PAD101 EudraCT2012-001019-22	PAD	VEGF-DdNdC	Ad	i.m.	30	Gene transfer 1-2 days before operation to improve distal runoff from surgical bypass graft in PAD	Recruiting
Trials using therapeutic vascular growth with aim for reduced side-effects							
KAT301 EudraCT2008-003295-22	CAD	VEGF-DdNdC	Ad	i.myo.(cat)	30	Stimulation of both angiogenesis and lymphangiogenesis to improve cardiac fluid removal and decrease edema	Results pending
Trials with mitogenic and multifunctional growth factors							
ASPIRE	CAD	FGF-4	Ad	i.c.(cat)	100	Phaselll study, 3xdosage compared to previous AGENT-2 trial	Recruiting
AWARE	CAD	FGF-4	Ad	i.c. (cat)	300	only women recruited	Planned
NCT02276937	PAD	FGF-2	SeV	i.m.	60	SeV used	Recruiting
NCT01548378	PAD	HGF	Pl	i.m.	200	A large HGF trial	Results pending
NCT02144610	PAD	HGF	Pl	i.m.	500	A large HGF trial	Recruiting

Ad, adenovirus; cat, catheter-mediated; GP, gene product; i.a., intra-arterial; i.c., intracoronary; i.m., intramuscular; i.myo., intramyocardial; Pl, plasmid; RV, retrovirus; SeV, sendai-virus; tct, thoracotomy.

Yla-Herttuala SY et al, Eur Heart J, 2017

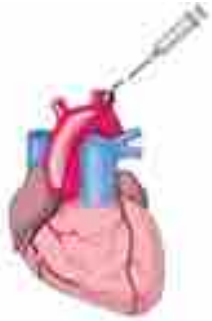
Leçons des stratégies de thérapie génique

- Sélection des patients
- Méthodes d'administration du gène
- Vecteurs
- Critères cliniques d'évaluation: Les mesures objectives d'évaluation, telles que la TEP, l'IRM, l'ECG et les ultrasons, devraient être privilégiées par rapport aux mesures subjectives ou non spécifiques, telles que les tests d'effort ou les questionnaires sur la qualité de vie
- Multi-approches?



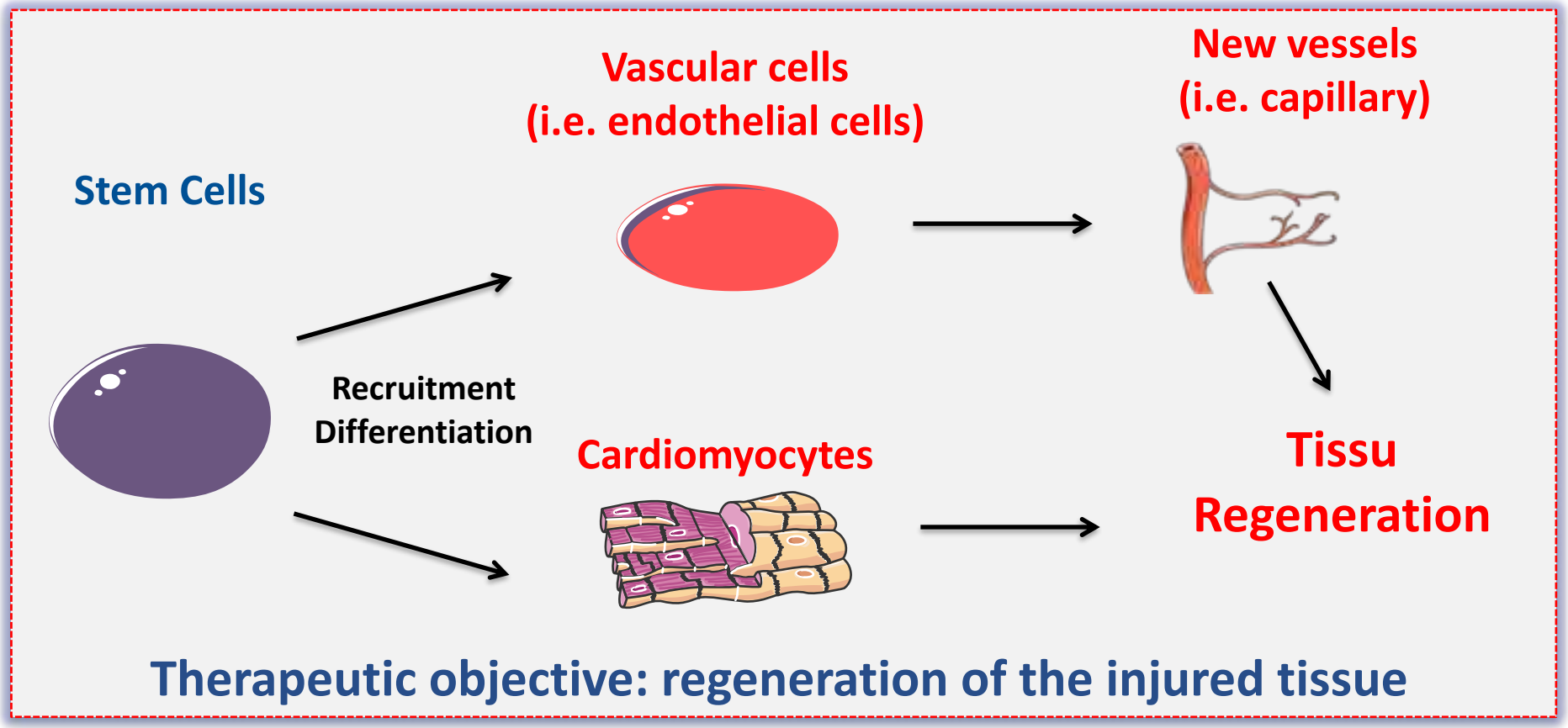
Yla-Herttuala SY et al, Eur Heart J, 2017

3-b Thérapie cellulaire



Ischemic cardiac diseases:
Acute Myocardial Infarction, Heart Failure

Ischemic vascular diseases (non coronary diseases):
Critical limb ischemia



Therapeutic objective: regeneration of the injured tissue

Thérapie cellulaire: cellules souches adultes

Patients with acute myocardial infarction, heart failure

Patients with critical limb ischemia

1- Adult Stem/progenitor cells

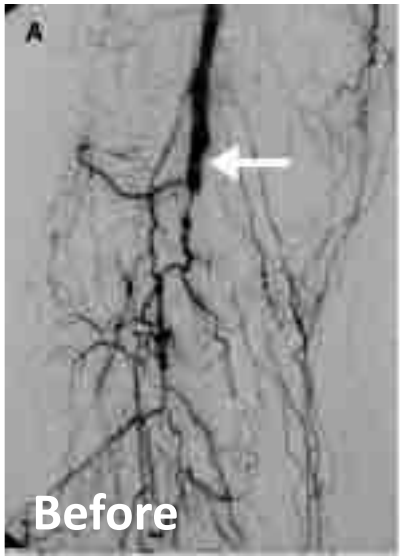
√ **Bone Marrow**: **Total, MNC, MSC, HSC, angiogenic cells (CD34, CD133, CXCR4 …)**

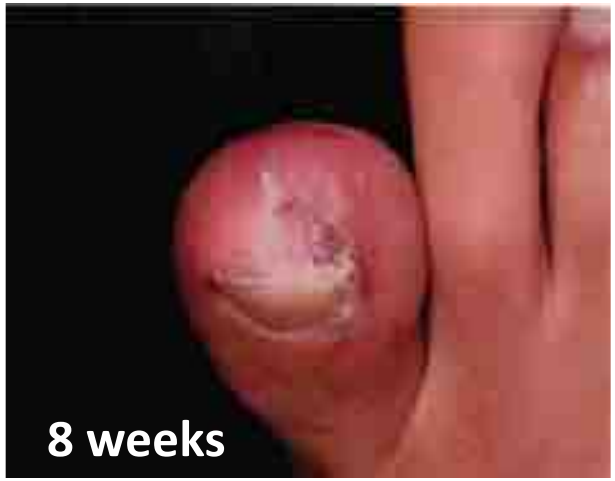
√ **Circulating cells: PB-derived MNC, CB-derived MNC/EPC/SMPC, angiogenic cells (monocytes, early EPC …)**

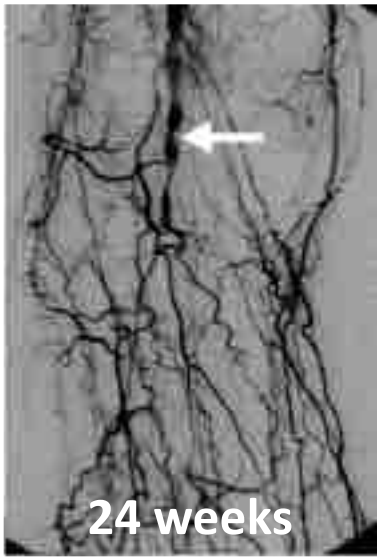
√ **Tissues: Heart (C-kit, Sca-1, CD34, cardiosphere), vessel wall, adipose tissue (SVF,ADSC), skeletal muscle…**

Silvestre JS et al, Physiol Rev, 2013

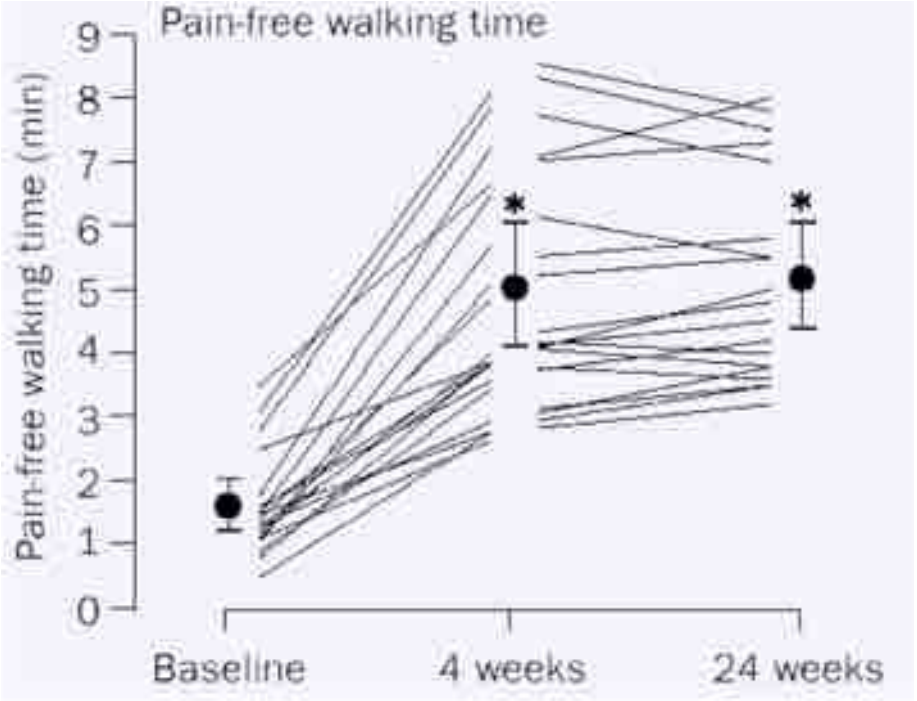
3-b-1 Thérapie cellulaire et ischémie critique du membre inférieur







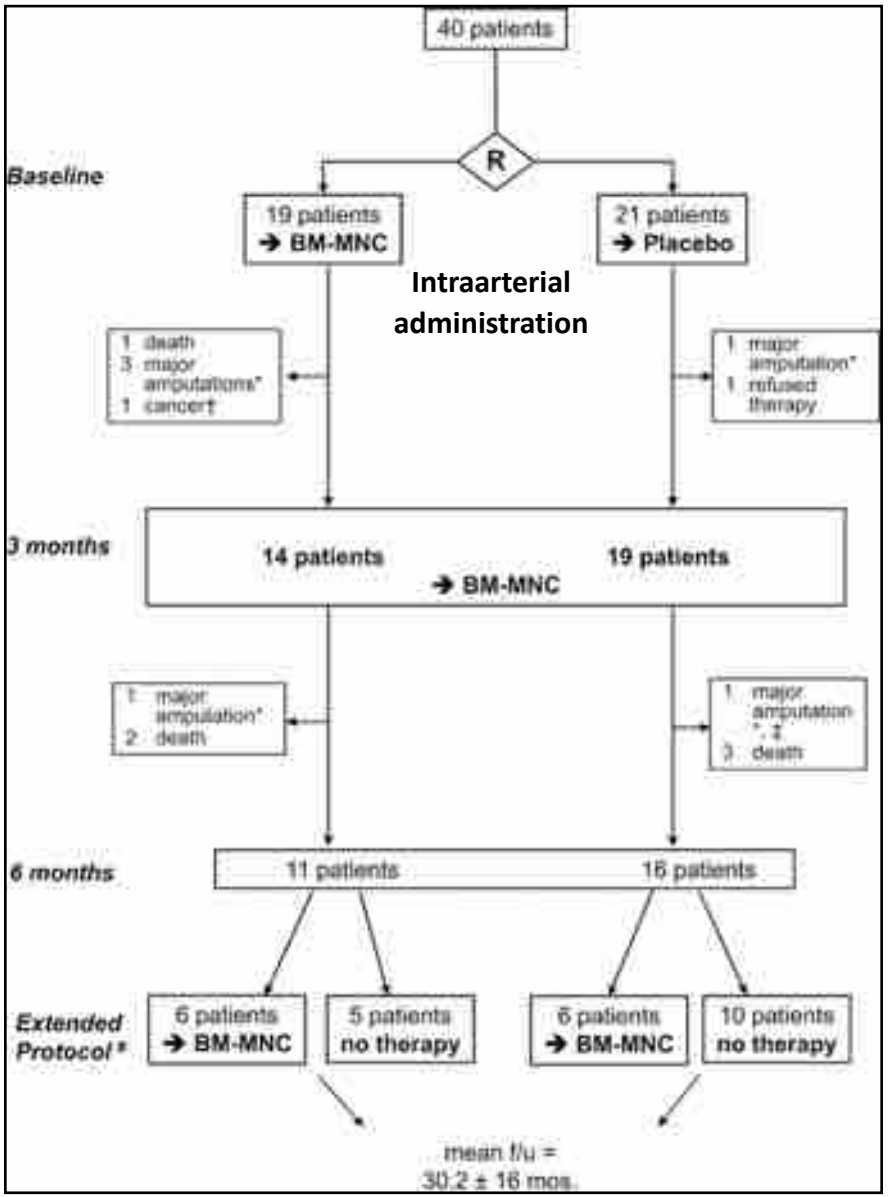
22-29 patients, chronic limb ischemia
BM-MNC (10^9) in the leg



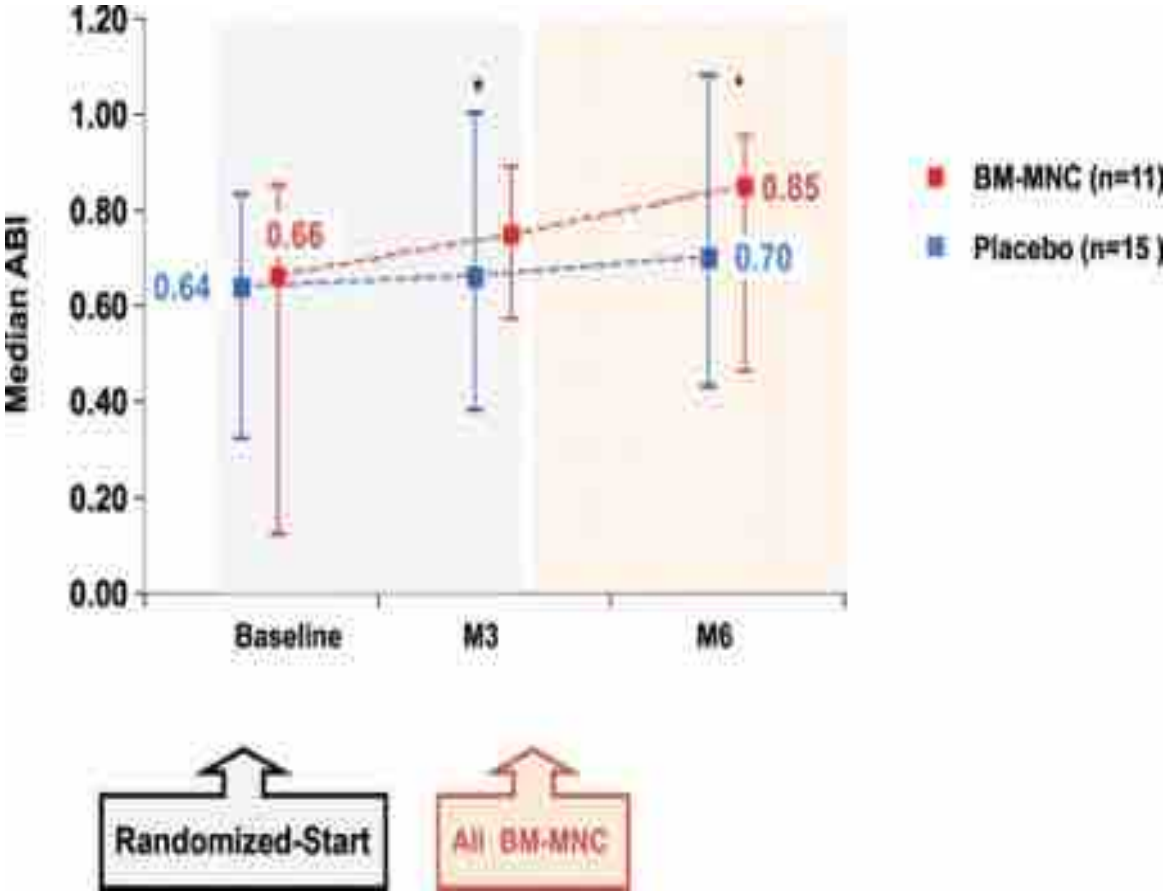
Tateishi-Yujama et al, The Lancet, 2002

Cellules mononuclées médullaires et Ischémie critique

√ Flow chart of the POVASA study



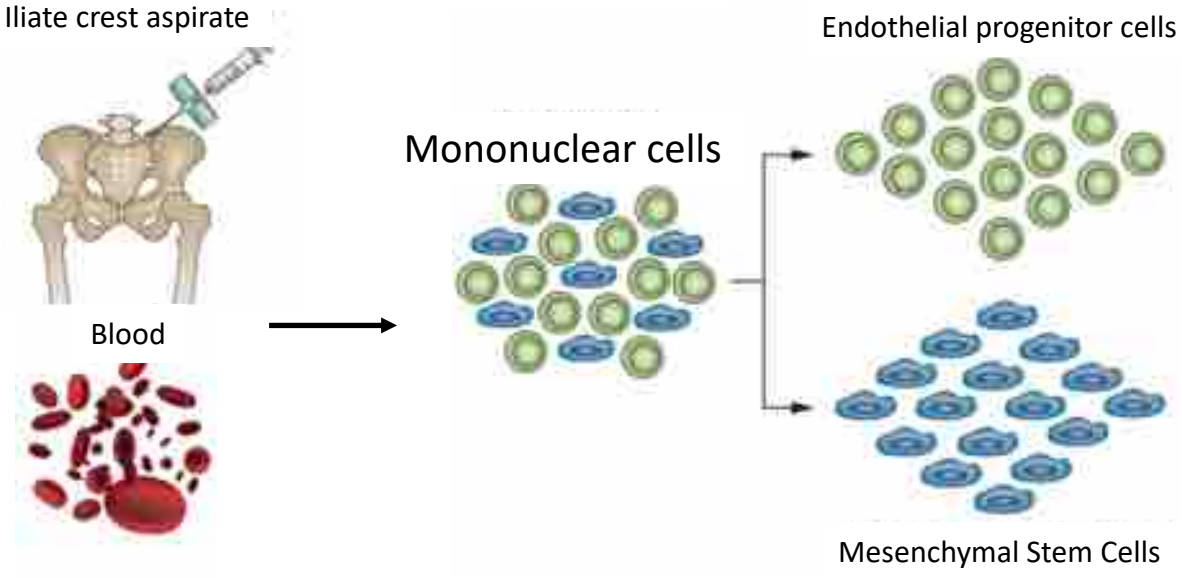
√ Ankle-brachial index



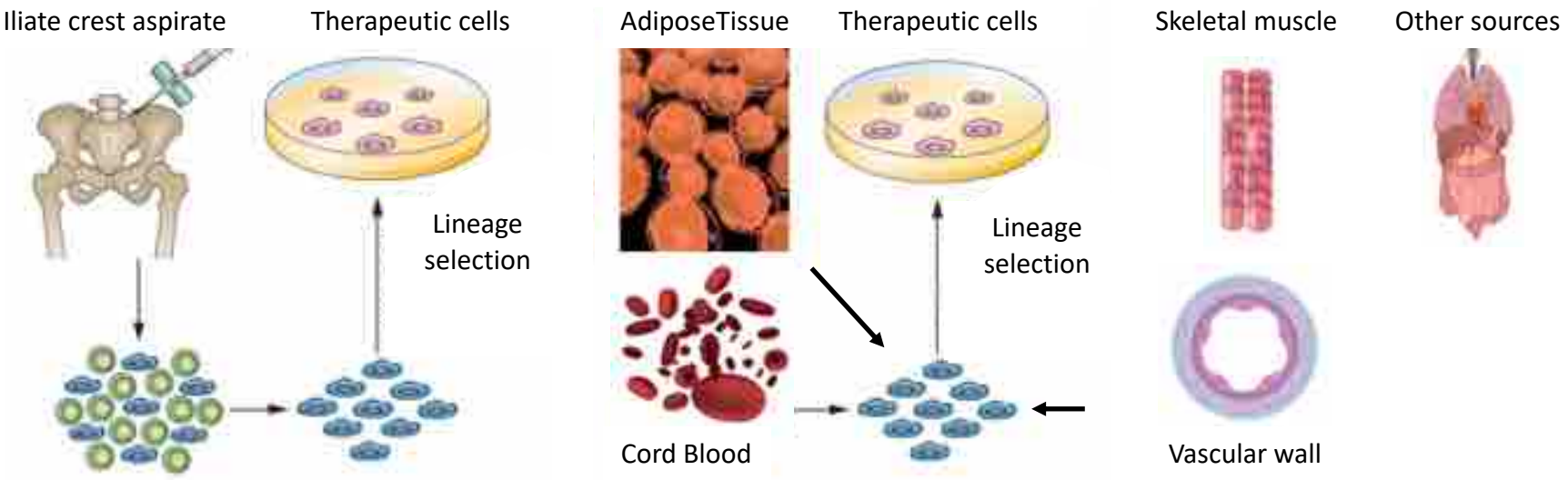
Walter DH et al, Circ Cardiovasc Interv, 2011

Différentes sources de cellules adultes thérapeutiques

First Generation : Bone Marrow/Blood



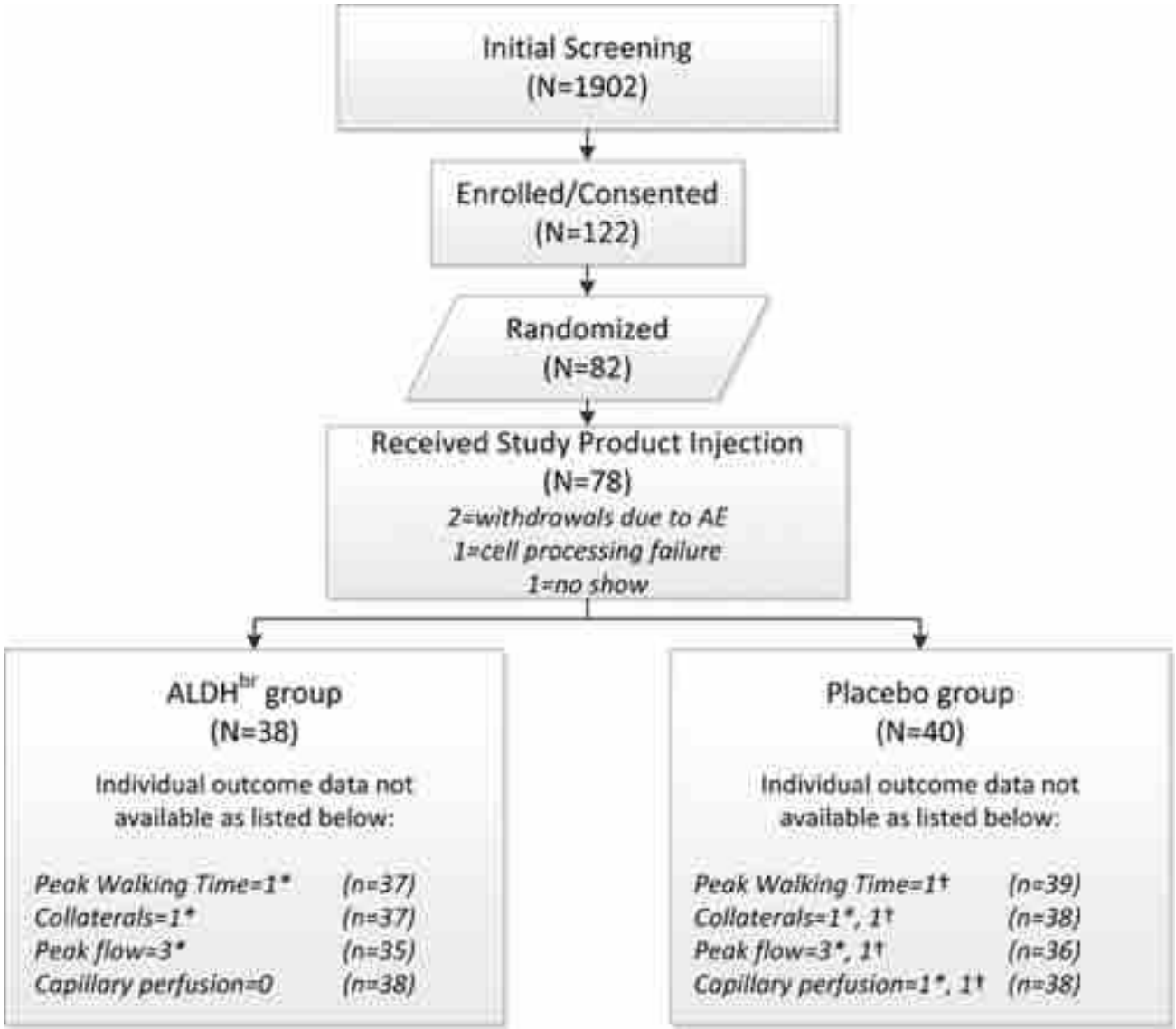
Second Generation : Alternative sources of therapeutic cells



Autres sources de cellules souches adultes: ALDH bright cells

PACE was a phase II randomized, double-blind, placebo-controlled clinical trial designed to evaluate the effect of administration of ALDHbr cells versus cell-free placebo in individuals with PAD and intermittent claudication

Bone marrow–derived aldehyde dehydrogenase bright (ALDHbr) are characterized by the expression of high levels of the cytosolic enzyme aldehyde dehydrogenase, contain potent stem and progenitor cells capable of ischemic repair and include hematopoietic, endothelial, and mesenchymal cell types.



Perin et al, Circulation, 2017

NO EFFECTS

Autres sources de cellules souches adultes: ADSC

Fat Pad

Aspirate/Wash/Digestion

Right atrium
Epicardial fat
Pericardial fat, subcutaneous fat,
(Naftali-Shani N et al, JAHA, 2013)

Fat Graft

Cell culture

Stroma Vascular Fraction

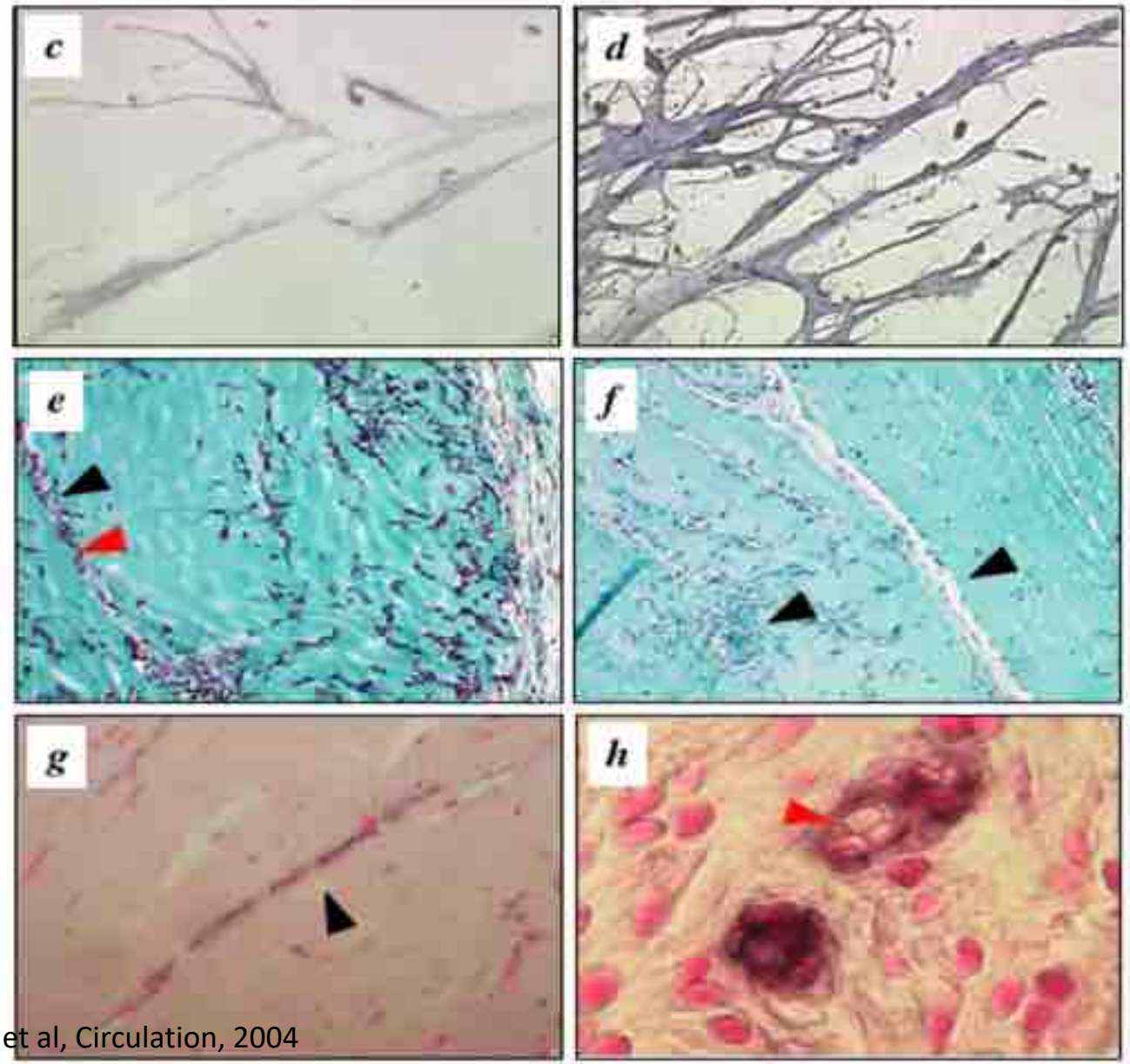
CD34+, CD45low, CD14low, CD13, CD31+

Therapeutic cells from adipose tissue origin

Adipose Derived Stem Cells

CD34+, CD31-, CD45-, CD105+

Autres sources de cellules souches adultes: ADSC



Methylcellulose
+ CD31, + vWF

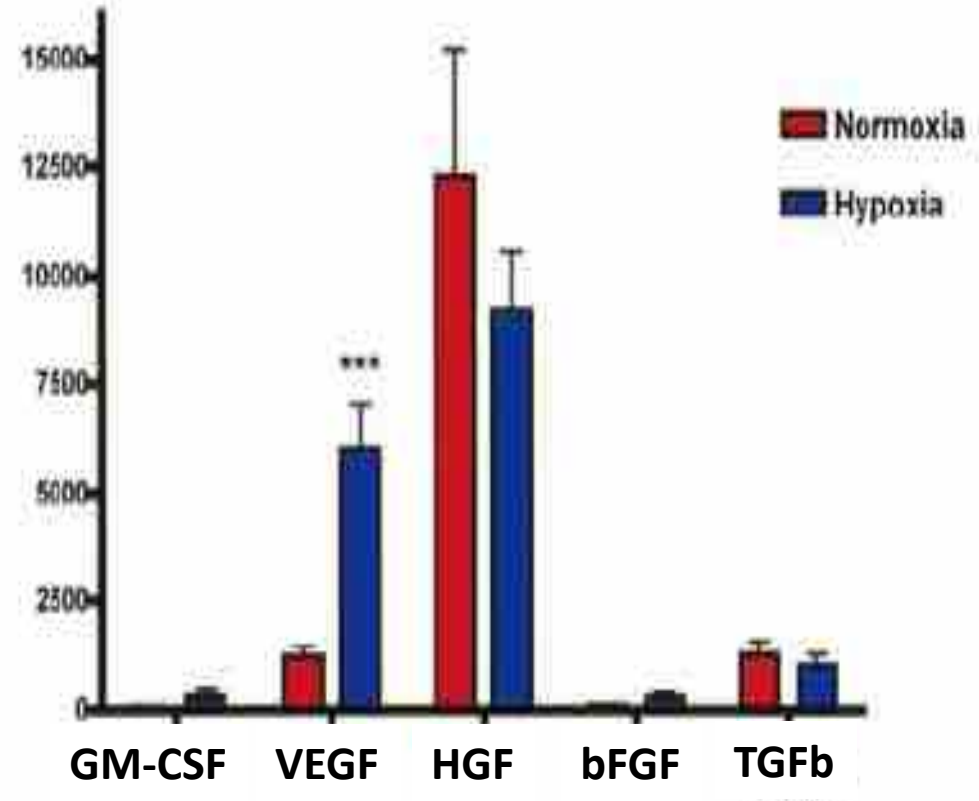
Matrigel

Matrigel +
CD31 humain
vWF

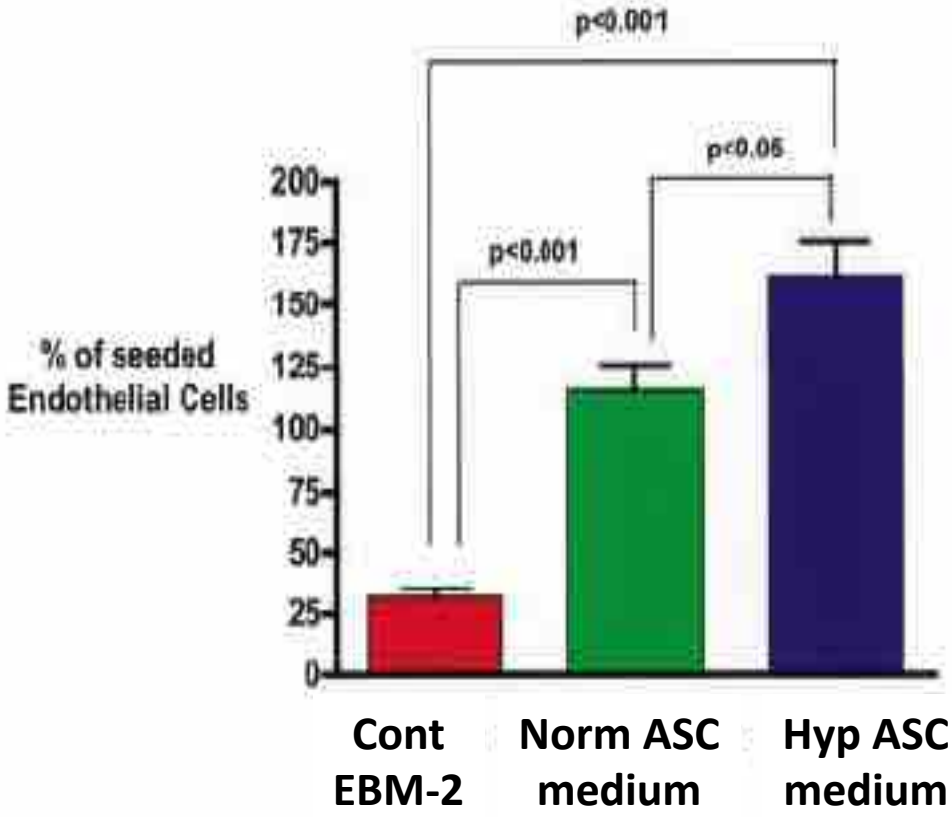
Planat V et al, Circulation, 2004

Autres sources de cellules souches adultes: ADSC

Sécrétion de GF - 72 heures

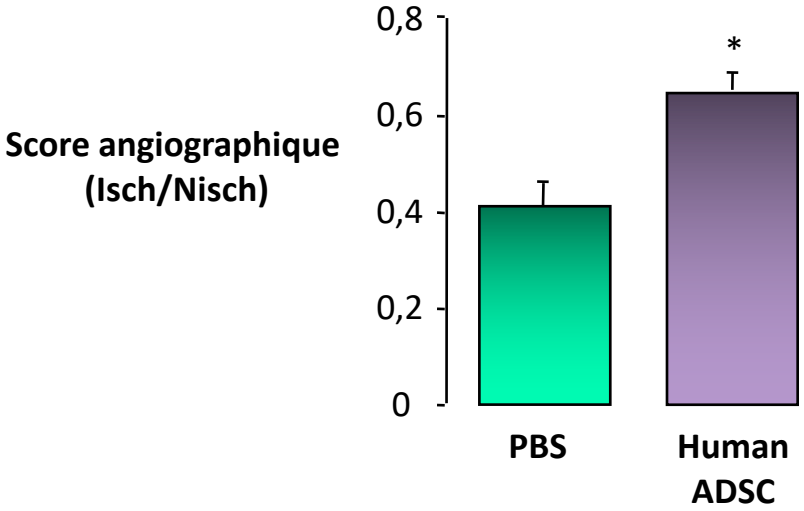


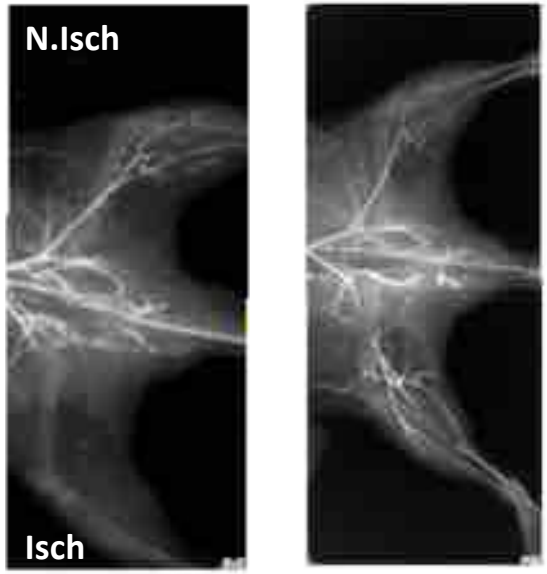
Nombre de cellules endothéliales

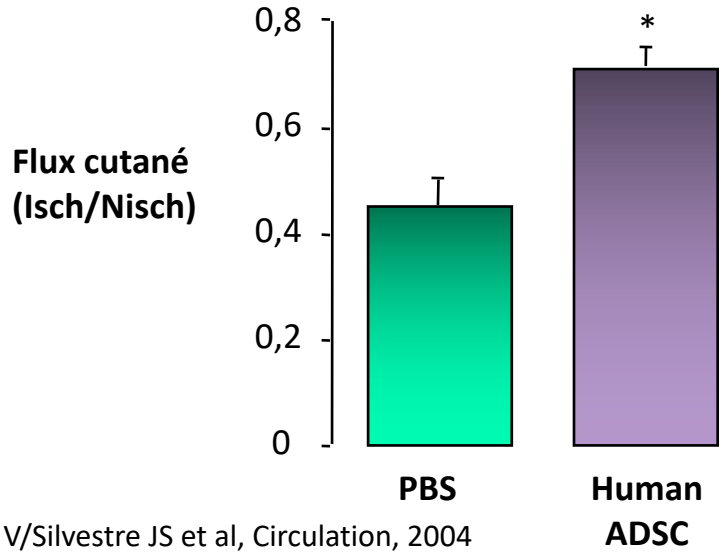


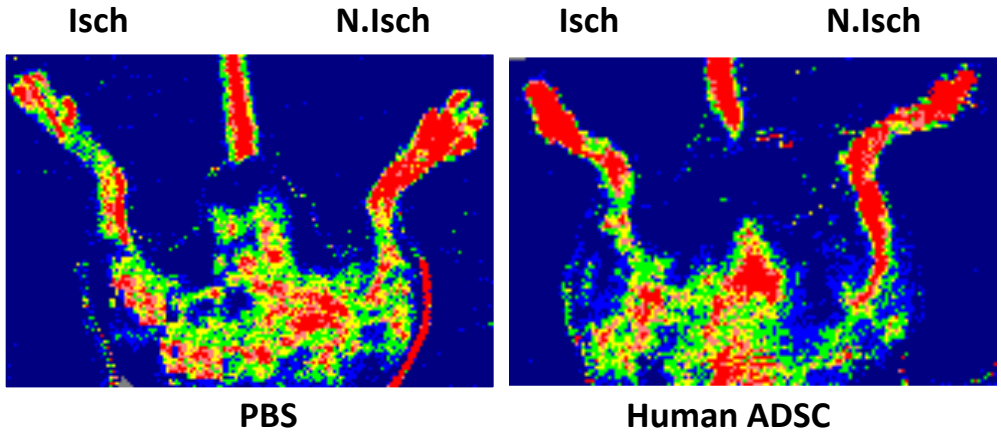
Rehman J et al, Circulation, 2004

Autres sources de cellules souches adultes: ADSC





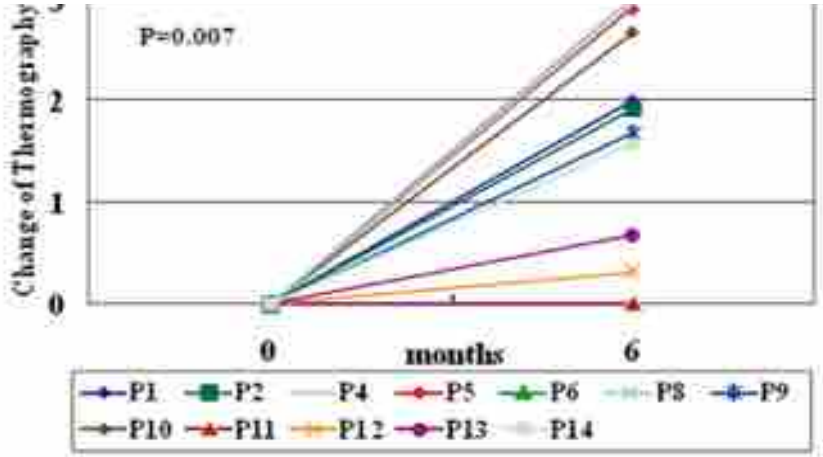


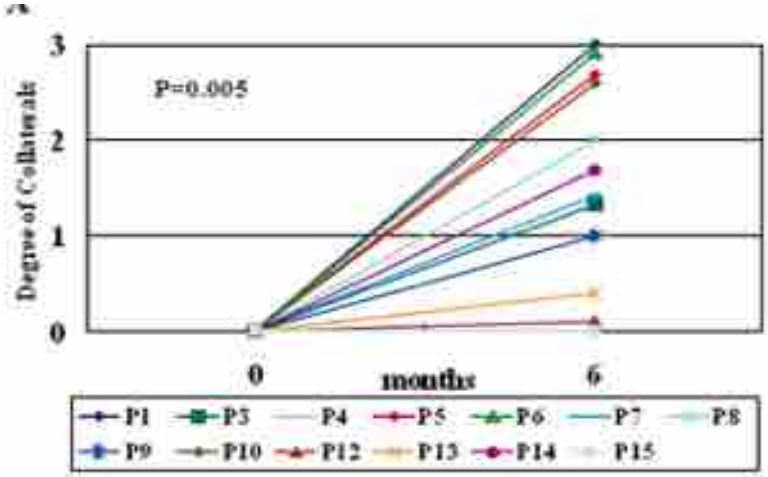


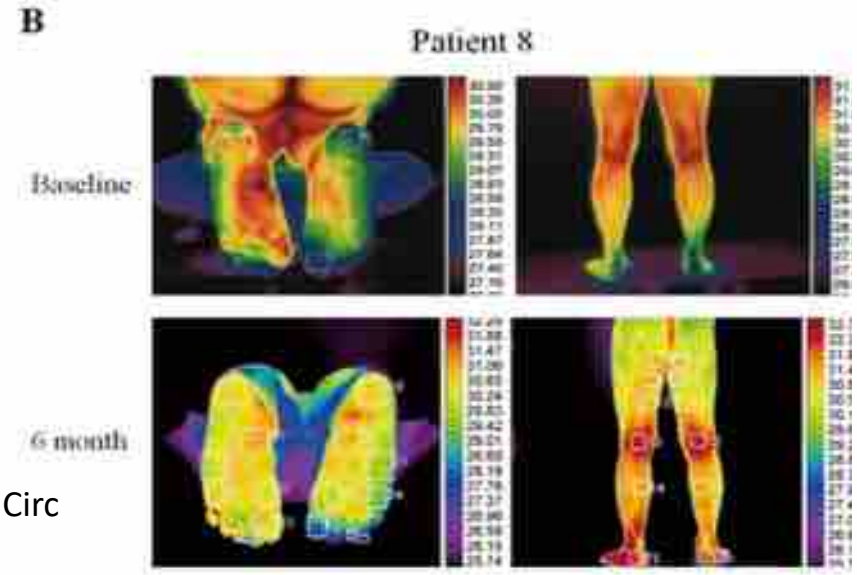
Planat-Benard V/Silvestre JS et al, Circulation, 2004

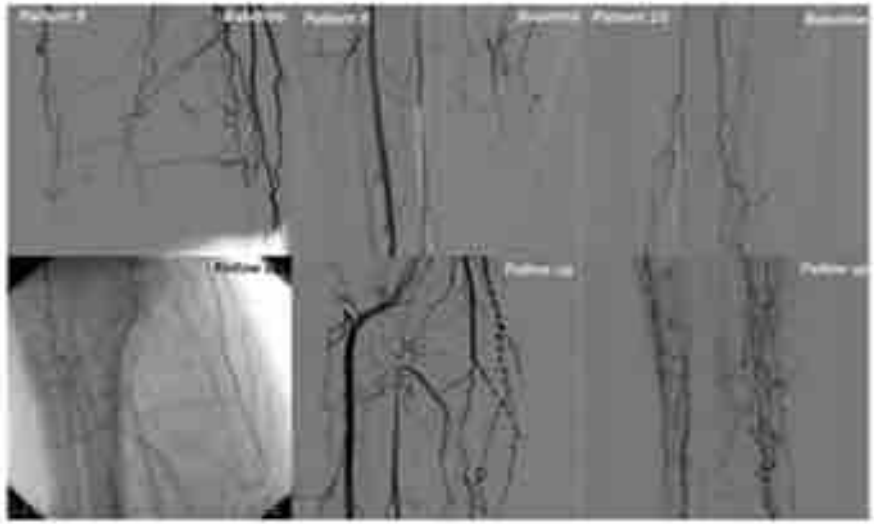
Autres sources de cellules souches adultes: ADSC

15 male CLI patients with ischemic resting pain in 1 limb with/without non-healing ulcers and necrotic foot. ATMSC were isolated from adipose tissue of thromboangiitis obliterans (TAO) patients (B-ATMSC) and healthy donors (control ATMSC)







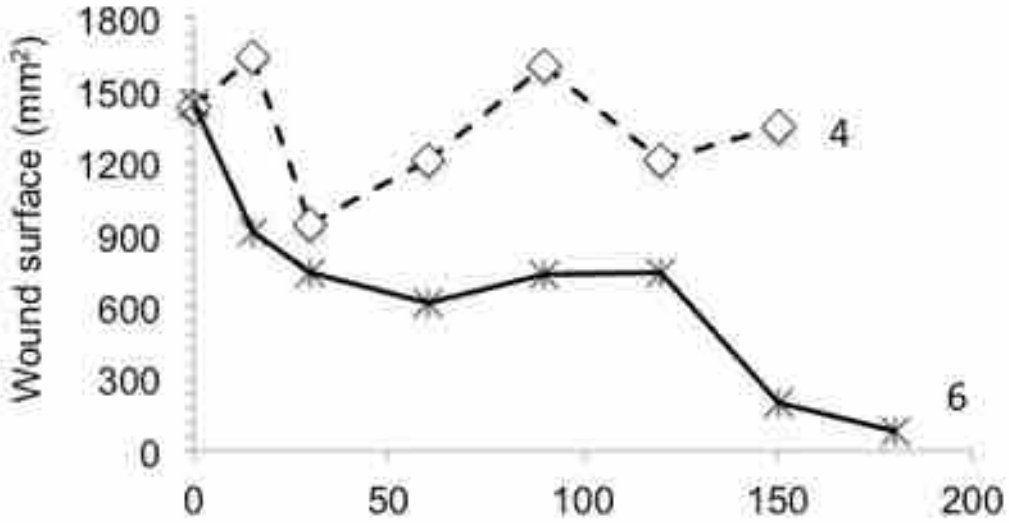


Lee HC, Circ J, 2012

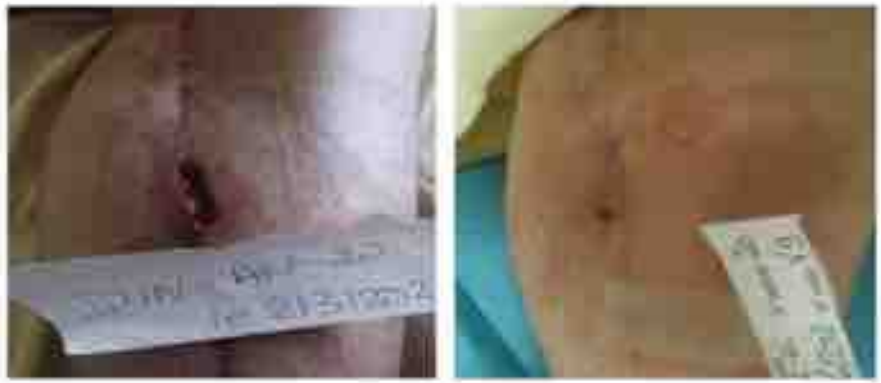
Autres sources de cellules souches adultes: ADSC

Seven patients: rest pains of ischaemic origin; ankle systolic oxygen pressure lower than 50 mmHg or the first toe systolic oxygen pressure lower than 30 mmHg; not suitable candidates for vascular or endovascular surgery.

10^8 ADSC were implanted by intramuscular injections into the internal and external gastrocnemius and anterior compartment of the ischemic leg



Patient 6



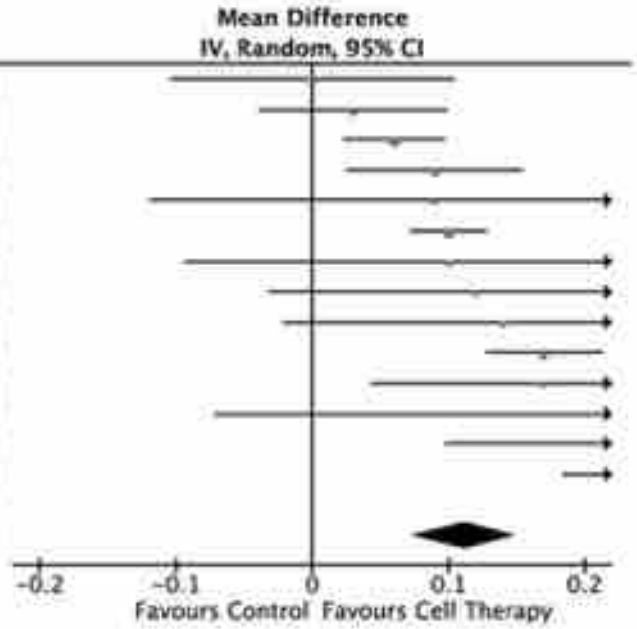
Bura-Rivière A et al, Cell Transplantion, 2014

Thérapies cellulaires – méta-analyses, Ischémie critique

Primary analysis: ABI

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Losordo et al. 2012 HD	0.1	0.05	9	0.1	0.175	12	7.3%	0.00 [-0.10, 0.10]
Teraa et al. 2015	0.11	0.2	81	0.08	0.24	79	10.6%	0.03 [-0.04, 0.10]
Arai et al. 2006	0.53	0.06	13	0.47	0.03	12	14.0%	0.06 [0.02, 0.10]
Lu et al. 2008	0.7	0.11	22	0.61	0.11	23	11.0%	0.09 [0.03, 0.15]
Walter el al. 2011	0.75	0.24	19	0.66	0.42	21	2.7%	0.09 [-0.12, 0.30]
Lu et al. 2011 BM MNC	0.65	0.034	19	0.55	0.071	37	14.9%	0.10 [0.07, 0.13]
Losordo et al. 2012 LD	0.2	0.225	7	0.1	0.175	12	3.1%	0.10 [-0.09, 0.29]
Huang et al. 2005	0.63	0.25	23	0.51	0.28	24	4.5%	0.12 [-0.03, 0.27]
Ozturk et al. 2012	0.87	0.24	20	0.73	0.28	20	4.1%	0.14 [-0.02, 0.30]
Lu et al. 2011 BM MSC	0.72	0.078	18	0.55	0.071	37	13.4%	0.17 [0.13, 0.21]
Gupta et al. 2013	0.76	0.15	10	0.59	0.14	10	5.7%	0.17 [0.04, 0.30]
Skora et al. 2015	0.52	0.52	16	0.3	0.29	16	1.5%	0.22 [-0.07, 0.51]
Mohammadzadeh et al. 2012	0.92	0.15	7	0.65	0.25	14	3.8%	0.27 [0.10, 0.44]
Szabo et al. 2013	0.36	0.3	10	-0.01	0.014	10	3.3%	0.37 [0.18, 0.56]
Total (95% CI)			**274**			**327**	**100.0%**	**0.11 [0.07, 0.15]**

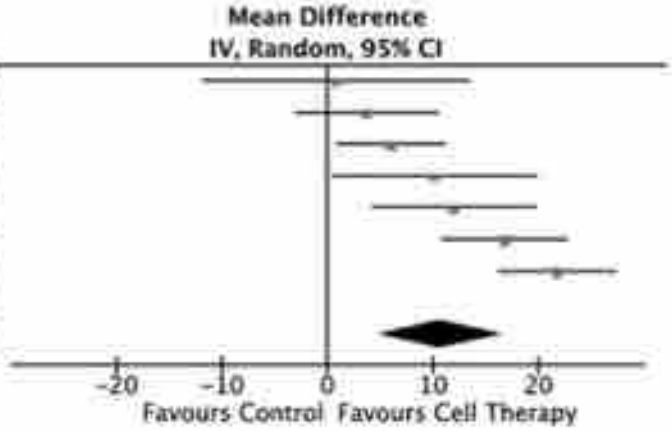
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 36.47$, df = 13 (P = 0.0005); $I^2 = 64\%$
Test for overall effect: Z = 5.75 (P < 0.00001)



Primary analysis: TcO_2

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Walter el al. 2011	40.5	23	19	39.7	17	21	10.0%	0.80 [-11.84, 13.44]
Teraa et al. 2015	10.4	23.3	81	6.7	20.1	79	15.1%	3.70 [-3.04, 10.44]
Arai et al. 2006	32	8	13	26	5	12	16.5%	6.00 [0.81, 11.19]
Szabo et al. 2013	6.6	12.6	10	-3.5	9.3	10	12.4%	10.10 [0.39, 19.81]
Ozturk et al. 2012	44.3	10.03	20	32.35	14.7	20	14.1%	11.95 [4.15, 19.75]
Lu et al. 2011 BM MNC	61	9.5	19	44.2	13	37	15.8%	16.80 [10.82, 22.78]
Lu et al. 2011 BM MSC	66	8	18	44.2	13	37	16.1%	21.80 [16.21, 27.39]
Total (95% CI)			**180**			**216**	**100.0%**	**10.74 [4.93, 16.54]**

Heterogeneity: $Tau^2 = 46.35$; $Chi^2 = 28.37$, df = 6 (P < 0.0001); $I^2 = 79\%$
Test for overall effect: Z = 3.62 (P = 0.0003)



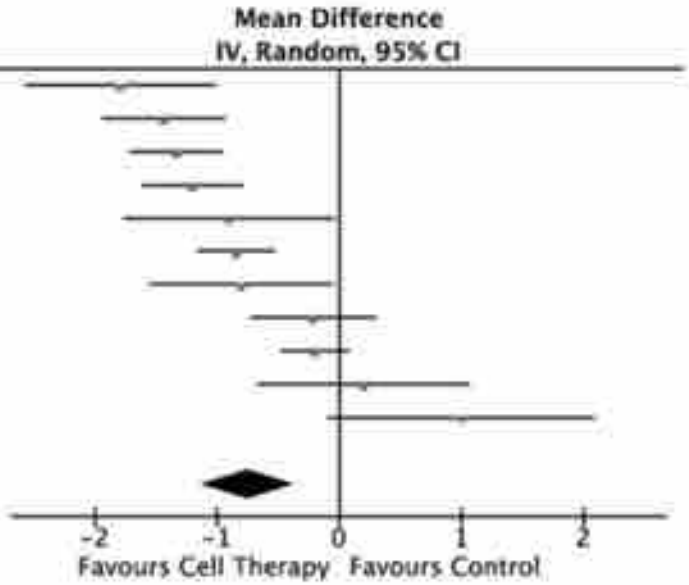
Rigato M et al, Circ Res, 2017

Thérapies cellulaires – méta-analyses, Ischémie critique

Primary analysis: pain score

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Huang et al. 2005	1.07	0.92	14	2.86	1.17	14	7.9%	-1.79 [-2.57, -1.01]
Lu et al. 2011 BM MSC	1.87	1	18	3.3	0.6	37	9.9%	-1.43 [-1.93, -0.93]
Lu et al. 2008	2.14	0.66	22	3.47	0.64	23	10.7%	-1.33 [-1.71, -0.95]
Lu et al. 2011 BM MNC	2.1	0.8	19	3.3	0.6	37	10.5%	-1.20 [-1.61, -0.79]
Losordo et al. 2012 LD	-1.3	0.6	7	-0.4	1.3	12	7.4%	-0.90 [-1.76, -0.04]
Ozturk et al. 2012	2.24	0.64	20	3.08	0.32	20	11.0%	-0.84 [-1.15, -0.53]
Walter el al. 2011	0.8	1	19	1.6	1.4	21	8.2%	-0.80 [-1.55, -0.05]
Barc et al. 2006	-1.41	0.7	14	-1.2	0.7	15	9.8%	-0.21 [-0.72, 0.30]
Arai et al. 2006	1.9	0.4	13	2.1	0.3	12	11.2%	-0.20 [-0.48, 0.08]
Losordo et al. 2012 HD	-0.2	0.7	9	-0.4	1.3	12	7.4%	0.20 [-0.67, 1.07]
Gupta et al. 2013	1	1.24	10	0	1.24	10	6.0%	1.00 [-0.09, 2.09]
Total (95% CI)			**165**			**213**	**100.0%**	**-0.74 [-1.12, -0.36]**

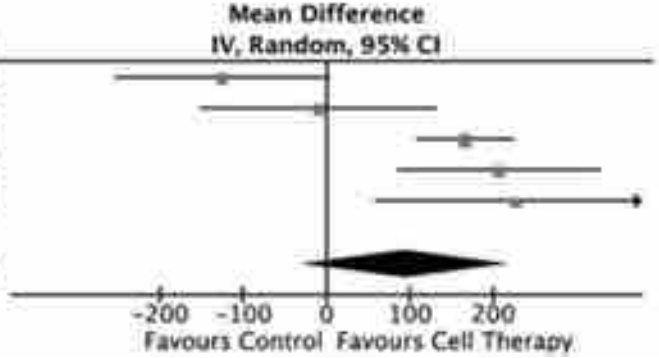
Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 62.13$, df = 10 ($P < 0.00001$); $I^2 = 84\%$
Test for overall effect: Z = 3.84 (P = 0.0001)



Primary analysis: Pain-free walking distance

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Losordo et al. 2012 LD	-16.7	92.7	7	108.2	191.8	12	19.8%	-124.90 [-253.32, 3.52]
Losordo et al. 2012 HD	98	138.6	9	108.2	191.8	12	19.0%	-10.20 [-151.54, 131.14]
Lu et al. 2008	369.3	111	22	203.3	85.5	23	23.8%	166.00 [107.93, 224.07]
Dash et al. 2009	284.44	212.1	12	78.22	35.35	12	20.2%	206.22 [84.56, 327.88]
Huang et al. 2005	306.4	289.1	14	78.6	142.3	14	17.1%	227.80 [59.01, 396.59]
Total (95% CI)			**64**			**73**	**100.0%**	**93.73 [-30.05, 217.51]**

Heterogeneity: $Tau^2 = 15845.61$; $Chi^2 = 23.11$, df = 4 ($P = 0.0001$); $I^2 = 83\%$
Test for overall effect: Z = 1.48 (P = 0.14)



Rigato M et al, Circ Res, 2017

3-b-2 Thérapie cellulaire et pathologies cardiaques

Study	n	Cells delivered	Cell harvesting and manipulation			Cell delivery			Method of follow-up	Effect on ejection fraction
			Time of cell harvest	Method of purification	Incubation time	Vehicle	Route	Number of cells		
Trials in MI										
TOPCARE-AMI (2002)[15]	20	Bone marrow aspirate	3 days	Density-gradient separation and cell culture	ND	X-VIVO™ 10 (Lonza, Switzerland)	Intracoronary (OTW balloon); three injections of 10 ml	7.3×10^6	LV angiography	No change/ positive
BOOST (2004)[19]	60	Bone marrow aspirate	5 days	Ficoll (4% gelatine polysuccinate) density-gradient separation	6–8 h	10,000 U/l heparinized saline	Intracoronary (OTW balloon); four or five injections lasting 2–4 min	2.40×10^8	MRI	Positive
REPAIR-AMI (2006)[18]	204	Bone marrow aspirate	3–6 days	Ficoll–hypaque density-gradient centrifugation	Overnight at 23°C	X-VIVO™ 10 and 20% autologous serum	Intracoronary (OTW balloon within stent)	1.98×10^8	LV angiography	Positive
Leuven-AMI (2006)[16]	67	Bone marrow aspirate	24 h	Lymphoprep® (AXIS-SHIELD POC AS, Norway)	4–6 h	0.9% NS and 5% autologous serum	Intracoronary (OTW balloon within stent); three injections of 2–3 min)	4.80×10^8	MRI	No change
ASTAMI (2006)[17]	97	Bone marrow aspirate	4–7 days	Ficoll density gradient centrifugation	ND	Heparin-treated plasma	Intracoronary (OTW balloon within stent)	6.60×10^7	CT (SPECT)	No change
FINCELL (2008)[21]	80	Bone marrow aspirate	Morning of the day PCI was performed	Ficoll–hypaque density-gradient centrifugation	6 h	Unspecified medium and 50% autologous serum	Intracoronary (OTW balloon within stent)	3.60×10^9	Echo	Positive

Behfar, A et al, Nat. Rev. Cardiol, 2014

Cellules mononuclées médullaires et pathologies cardiaques

Study	n	Cells delivered	Cell harvesting and manipulation			Cell delivery			Method of follow-up	Effect on ejection fraction
			Time of cell harvest	Method of purification	Incubation time	Vehicle	Route	Number of cells		
FINCELL (2008)[41]	80	Bone marrow aspirate	Morning of the day PCI was performed	Ficoll–hypaque density-gradient centrifugation	6 h	Unspecified medium and 50% autologous serum	Intracoronary (OTW balloon within stent)	3.60×10^8	Echo	Positive
HEBE (2011)[42]	200	Bone marrow aspirate	<8 days	Lymphoprep®	ND	Sodium heparin and 4% HAS	Intracoronary (OTW balloon); three injections lasting 3 min	2.96×10^8	MRI	No change
TIME (2012)[54]	120	Bone marrow aspirate	3 or 7 days	Sepax® cell-processing system (Biosafe Group SA, Switzerland)	<12 h	Normal saline and 5% HAS	Intracoronary (OTW balloon); six injections of 5 ml	1.50×10^8	MRI	No change
Late-TIME (2011)[55]	87	Bone marrow aspirate	2–3 weeks	Sepax® cell-processing system	<12 h	Normal saline and 5% HAS	Intracoronary (OTW balloon; six injections of 5 ml)	1.50×10^8	MRI	No change
Trials in CHF										
TOPCARE-CHD (2006)[50]	92	BMMNCs or CPCs	3 months after MI	Ficoll density-gradient separation and cell culture	ND	10,000 U/l heparinized saline and a bolus of abciximab (glycoprotein IIb/IIIa receptor antagonist – 0.25 mg/kg)	Intracoronary (OTW balloon); three injections of 10 ml	BMMNCs: 2.1×10^6 CPCs: 2.2×10^7	Biplanar LV angiography	Positive/ no change
FOCUS-CCTRN (2012)[56]	92	BMMNCs	ND*	Sepax® cell processing system	<12 h	Normal saline +5% HAS	Intracoronary (OTW balloon); 15 injections of 0.2 ml	1.00×10^8	CT (SPECT)	No change

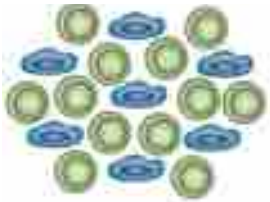
Multiples sources de cellules adultes thérapeutiques

First Generation : Bone Marrow/Blood

Iliate crest aspirate

Blood

Mononuclear cells



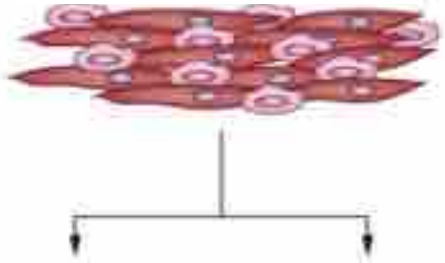
Endothelial progenitor cells

Mesenchymal Stem Cells

Adapted from Behfar, A et al, Nat. Rev. Cardiol, 2014

Second Generation : Cardiac Stem cells + Alternative sources of therapeutic cells

Resident cardiac Stem cells



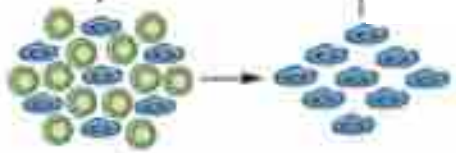
Isolated cardiac Stem cells

Cardiospheres

Iliate crest aspirate

Cardiopoietic stem cells

Lineage specification



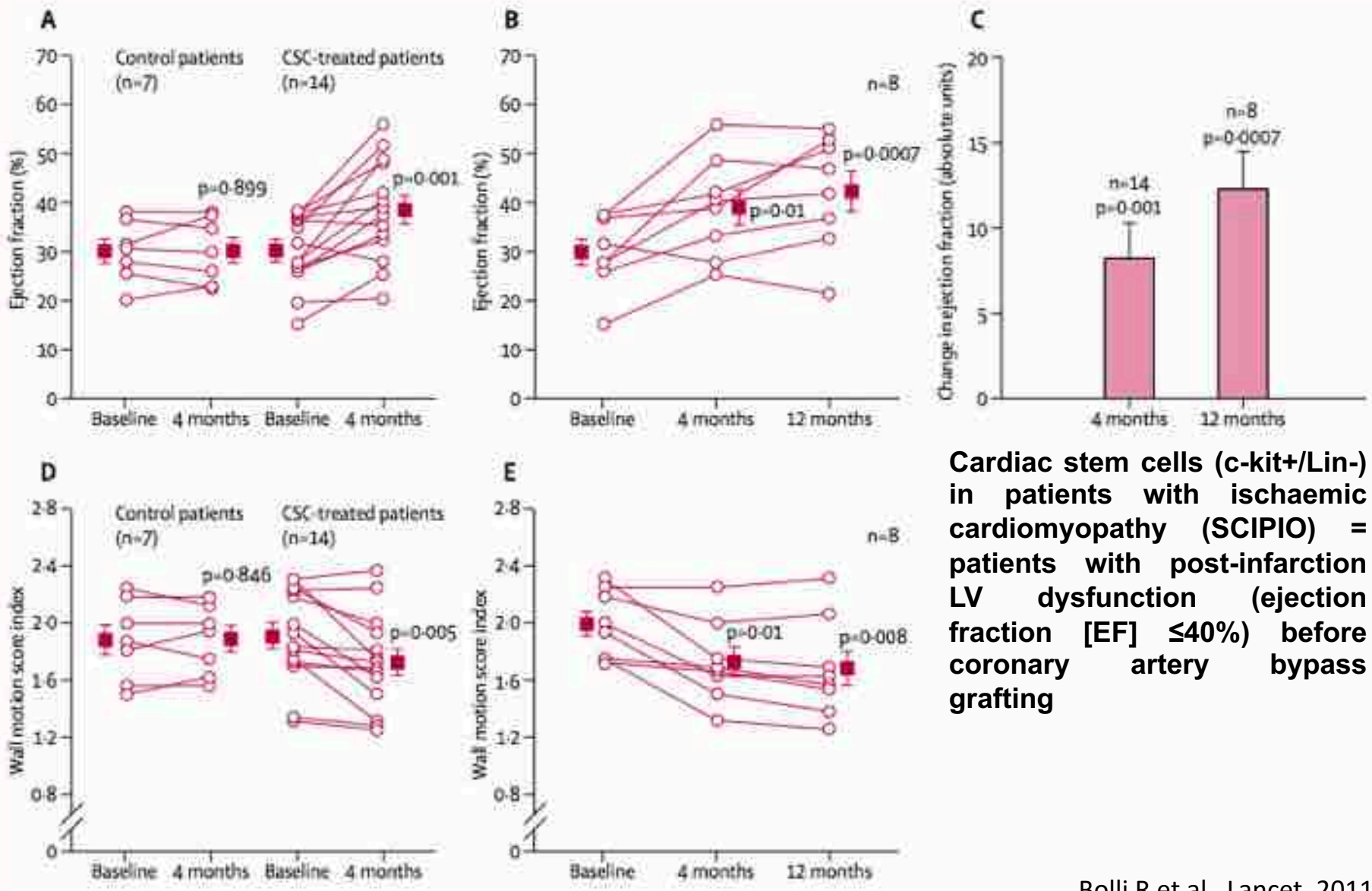
AdiposeTissue

Therapeutic cells

Lineage selection

Cord Blood

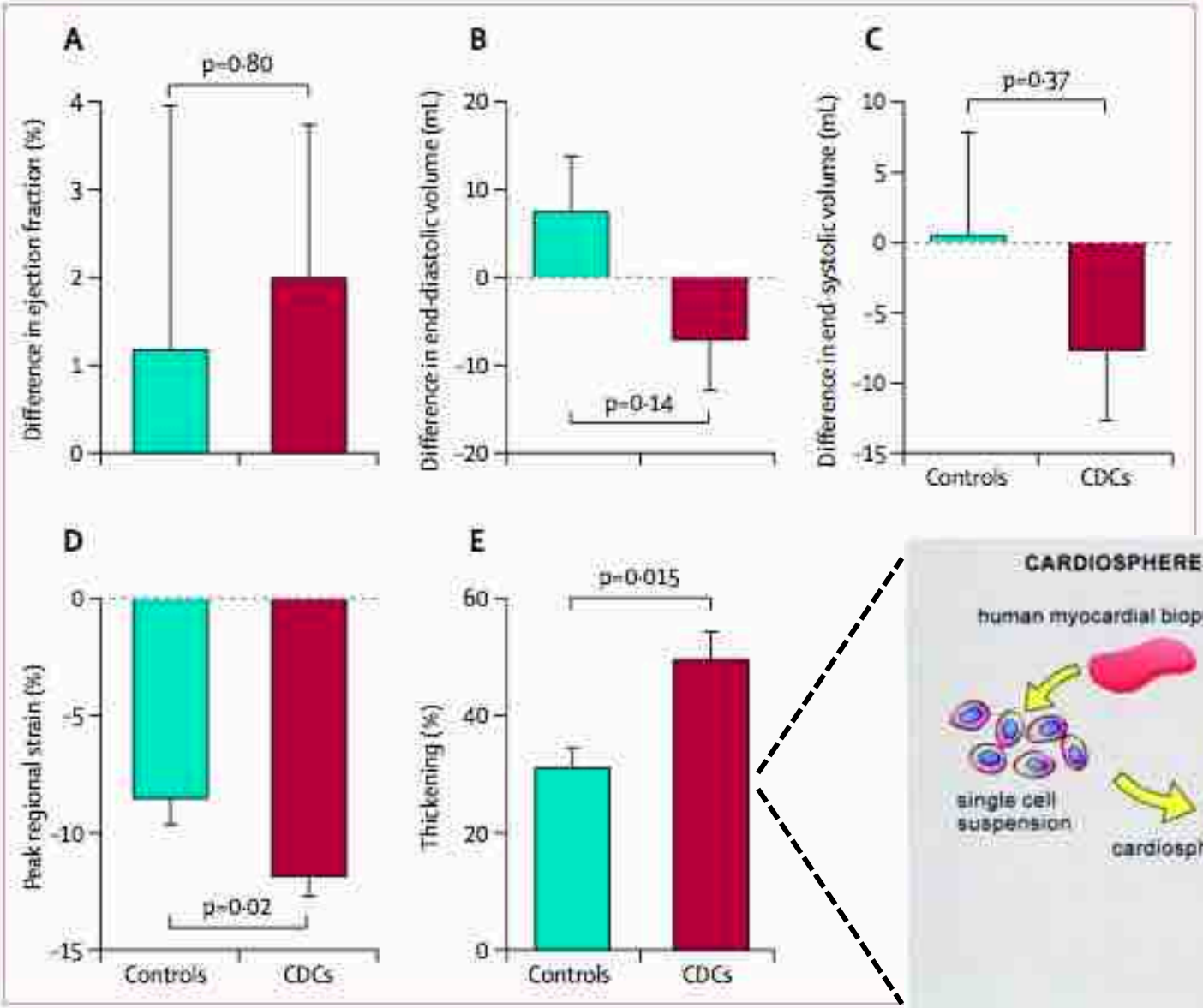
Autres sources de cellules souches adultes: cardiac SC

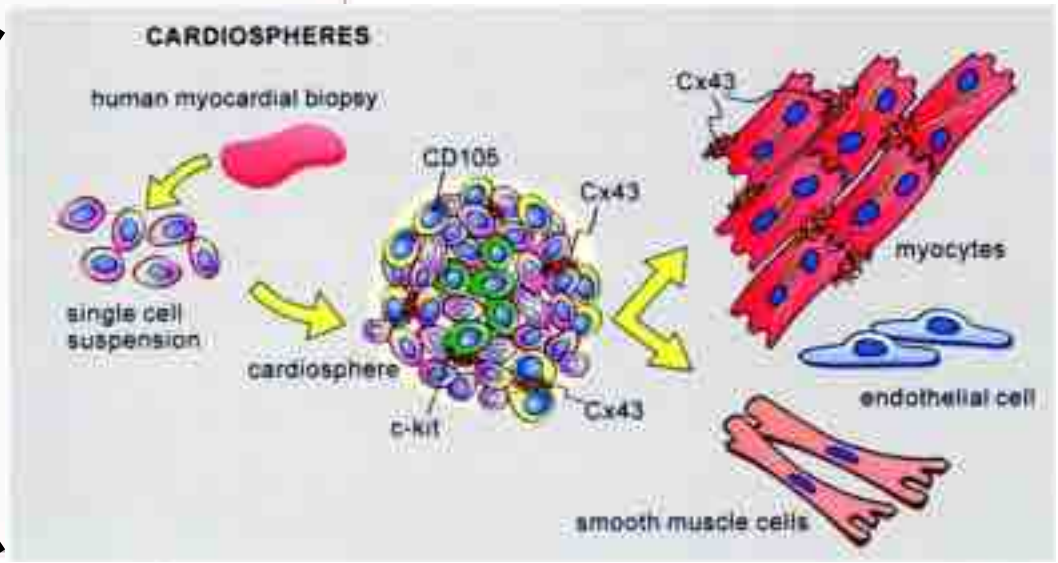


Cardiac stem cells (c-kit+/Lin-) in patients with ischaemic cardiomyopathy (SCIPIO) = patients with post-infarction LV dysfunction (ejection fraction [EF] ≤40%) before coronary artery bypass grafting

Bolli R et al , Lancet, 2011

Autres sources de cellules souches adultes: cardiac SC





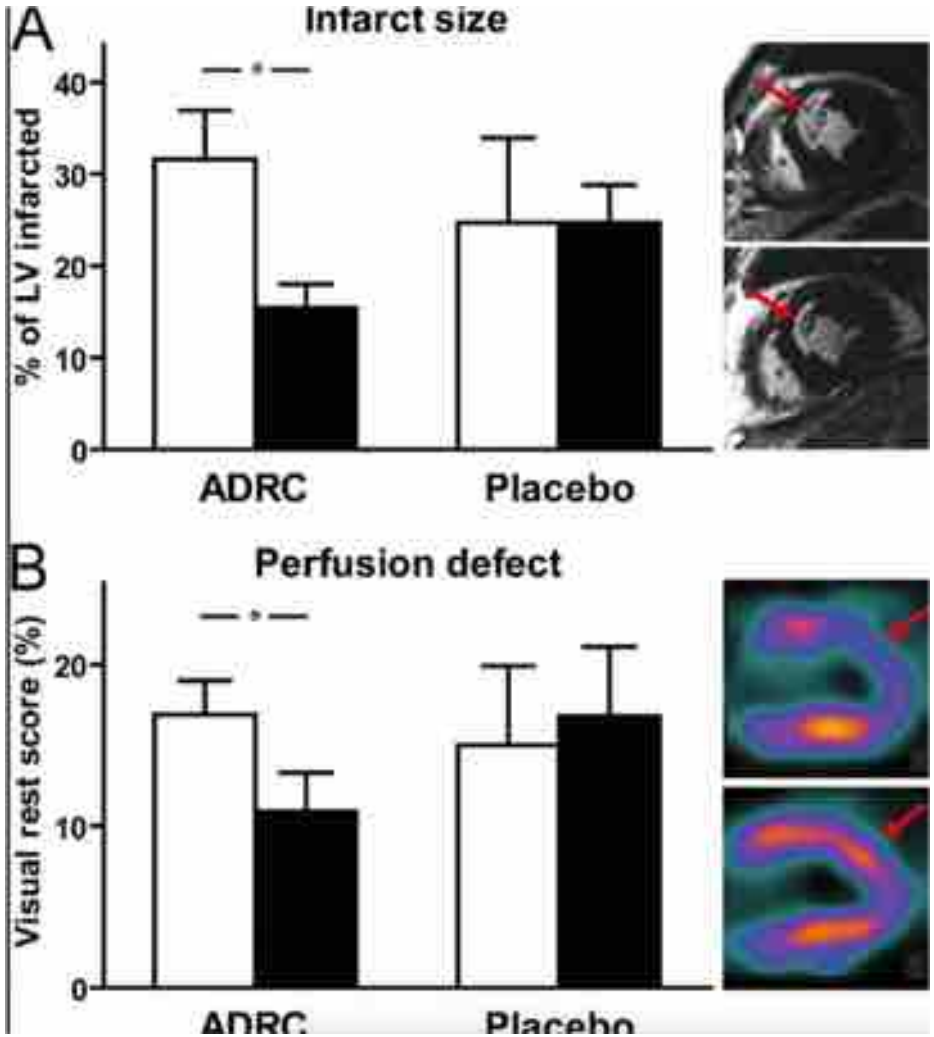
Prospective, randomised CArdiosphere-Derived aUtologous stem CElls to reverse ventricULar dySfunction (CADUCEUS) trial, patients were enrolled 2-4 weeks after myocardial infarction (with left ventricular ejection fraction of 25-45%)

Makkar RR, Lancet, 2012

Autres sources de cellules souches adultes: ADSC

The APOLLO trial is a randomized, double-blind, placebo-controlled, phase I/IIa study designed to assess the safety and feasibility of intracoronary infusion of ADRCs in the treatment of patients in the acute phase of a large ST-segment elevation acute myocardial infarction (STEMI)

1) liposuction to harvest ADRCs in the acute phase of an AMI is safe and feasible;
2) intracoronary infusion of freshly isolated ADRCs was safe and did not result in an alteration of coronary flow or any indication of microvascular obstruction;
3) no SAEs were related to the ADRC therapy; and
4) ADRC infusion resulted in a trend toward improved cardiac function, accompanied by a significant improvement of the perfusion defect and a 50% reduction of myocardial scar formation

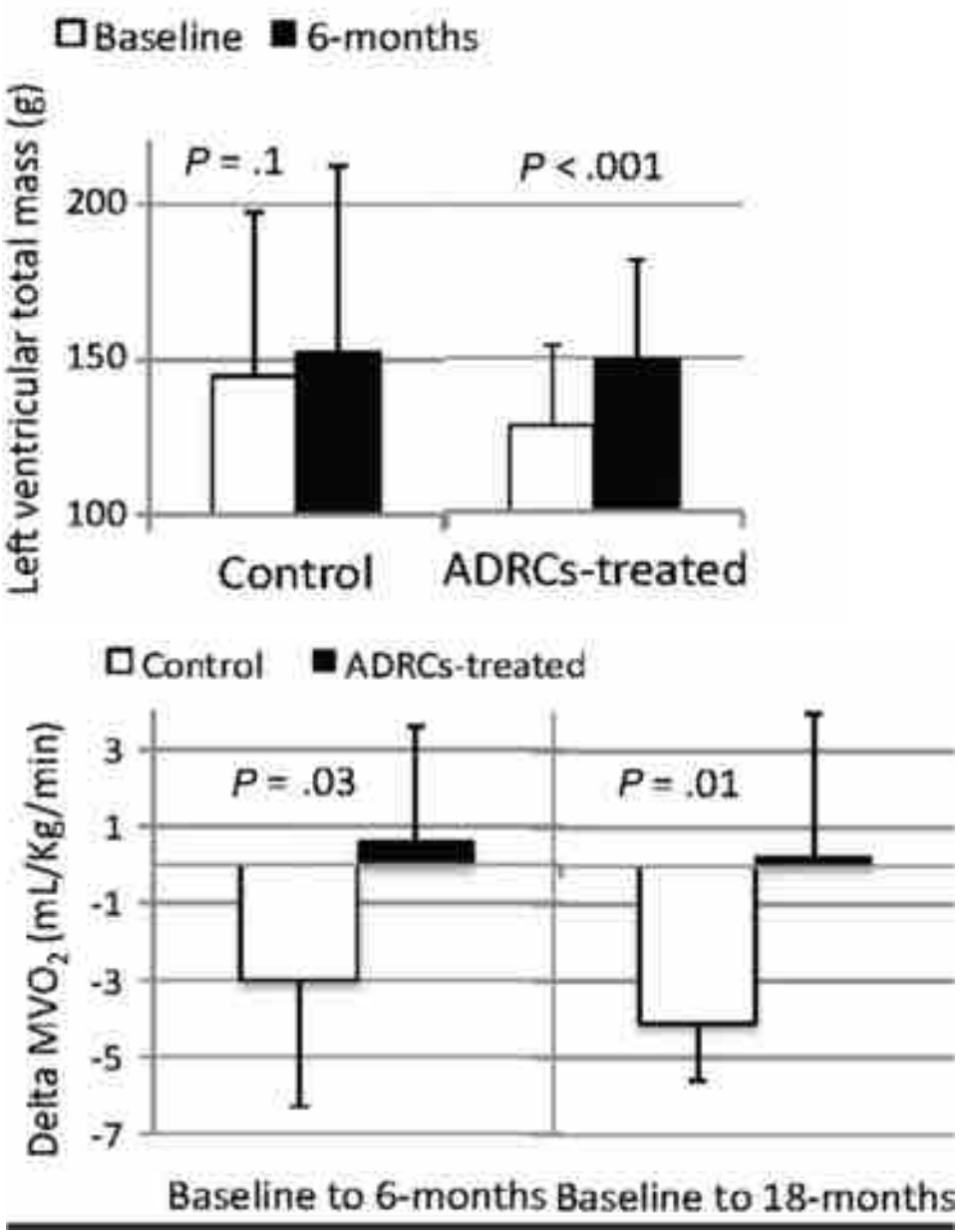


Houtgraaf JH, J Am Coll Cardiol, 2014

Autres sources de cellules souches adultes: ADSC

The PRECISE trial, randomized, placebo-controlled, double-blind trial Transendocardial injections of ADRCs in no-option Patients with ischemic cardiomyopathy, monitored up to 36 months.
Efficacy was assessed by echocardiography and single-photon emission computed tomography
(6, 12, and 18 months), metabolic equivalents and maximal oxygen consumption (MVO
2) (6 and 18 months), and cardiac magnetic resonance imaging (6 months).
21 ADRC-treated and 6 control patients.

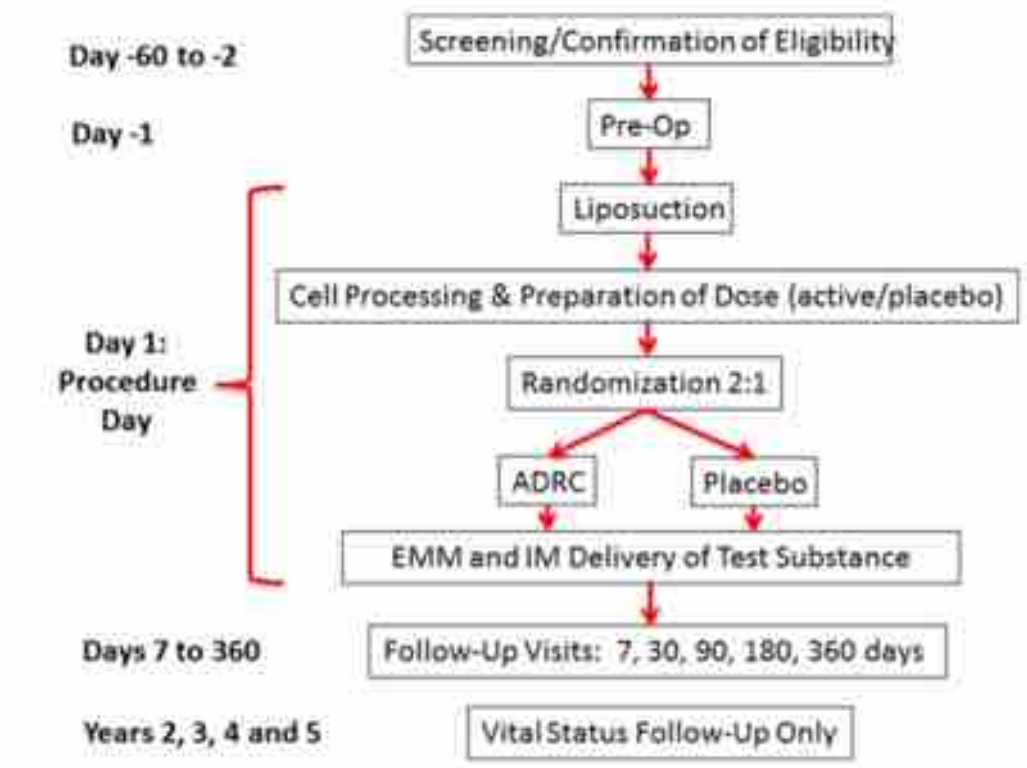
ADRCs may preserve ventricular function, myocardial perfusion, and exercise capacity in these patients.



Perin EC, Am J Heart, 2014

Autres sources de cellules souches adultes: ADSC

The Athena program consisted of two parallel, prospective, randomized (2:1, active: placebo), double-blind trials assessing intramyocardial (IM) ADRC delivery [40-million, $n = 28$ (ATHENA) and 80-million (ATHENA II) cells, $n = 3$]). Patients with an EF ≥20% but ≤45%, multivessel coronary artery disease (CAD) not amenable to revascularization, inducible ischemia, and symptoms of either angina (CCS II–IV) or heart failure (NYHA Class II–III) on maximal medical therapy were enrolled.

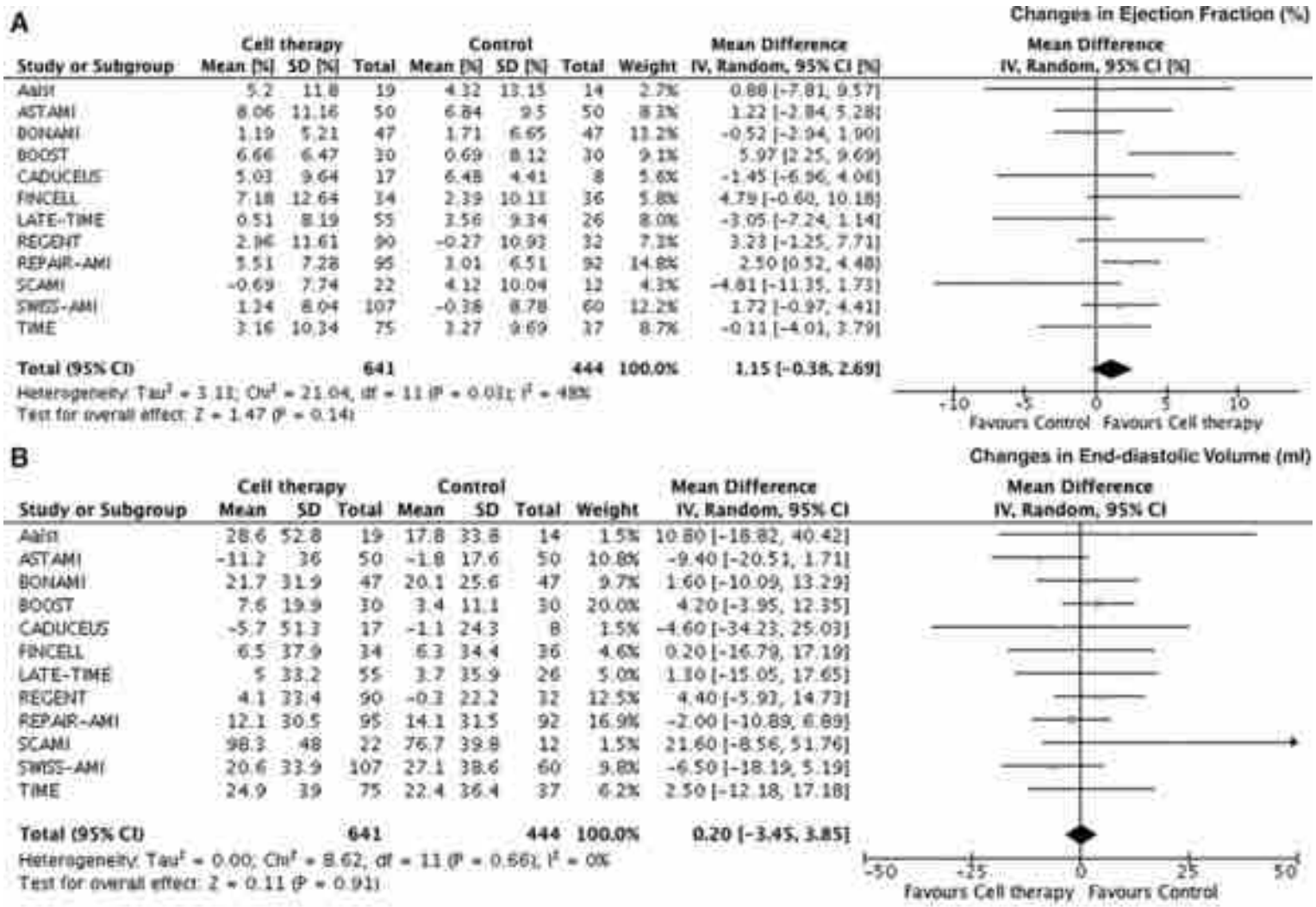


Improvement in both heart failure and angina symptoms and a reduction in heart failure hospitalizations. In contrast, there were no differences in LVEF or LV volumes by echocardiography. Autologous ADRCs may have greater benefit on symptoms, quality of life, and VO_2max, compared with the cardiac structural changes that were measured.

Henry TD, Catheter Cardiovasc Interv, 2017

Thérapies cellulaires – méta-analyses, Infarctus

Forest plot displaying changes in left ventricular ejection fraction, end-diastolic and end-systolic volumes in patients treated with intracoronary cell therapy after recent acute myocardial infarction.



A

Study or Subgroup	Cell therapy Mean [%]	SD [%]	Total	Control Mean [%]	SD [%]	Total	Weight	Mean Difference IV, Random, 95% CI [%]
Aalst	5.2	11.8	19	4.32	13.15	14	2.7%	0.88 [-7.81, 9.57]
ASTAMI	8.06	11.16	50	6.84	9.5	50	8.3%	1.22 [-2.84, 5.28]
BONAMI	1.19	5.21	47	1.71	6.65	47	11.2%	-0.52 [-2.94, 1.90]
BOOST	6.66	6.47	30	0.69	8.12	30	9.1%	5.97 [2.25, 9.69]
CADUCEUS	5.03	9.64	17	6.48	4.41	8	5.6%	-1.45 [-6.96, 4.06]
FINCELL	7.18	12.64	34	2.39	10.11	36	5.8%	4.79 [-0.60, 10.18]
LATE-TIME	0.51	8.19	55	3.56	9.34	26	8.0%	-3.05 [-7.24, 1.14]
REGENT	2.96	11.61	90	-0.27	10.92	32	7.3%	3.23 [-1.25, 7.71]
REPAIR-AMI	5.51	7.28	95	3.01	6.51	92	14.8%	2.50 [0.52, 4.48]
SCAMI	-0.69	7.74	22	4.12	10.04	12	4.3%	-4.81 [-11.35, 1.73]
SWISS-AMI	1.34	8.04	107	-0.38	8.78	60	12.2%	1.72 [-0.97, 4.41]
TIME	3.16	10.34	75	3.27	9.69	37	8.7%	-0.11 [-4.01, 3.79]
Total (95% CI)			**641**			**444**	**100.0%**	**1.15 [-0.38, 2.69]**

Heterogeneity: $Tau^2 = 3.11$; $Chi^2 = 21.04$, df = 11 (P = 0.03); $I^2 = 48\%$
Test for overall effect: Z = 1.47 (P = 0.14)

Changes in Ejection Fraction (%)
Mean Difference IV, Random, 95% CI [%]
-10 -5 0 5 10
Favours Control Favours Cell therapy

B

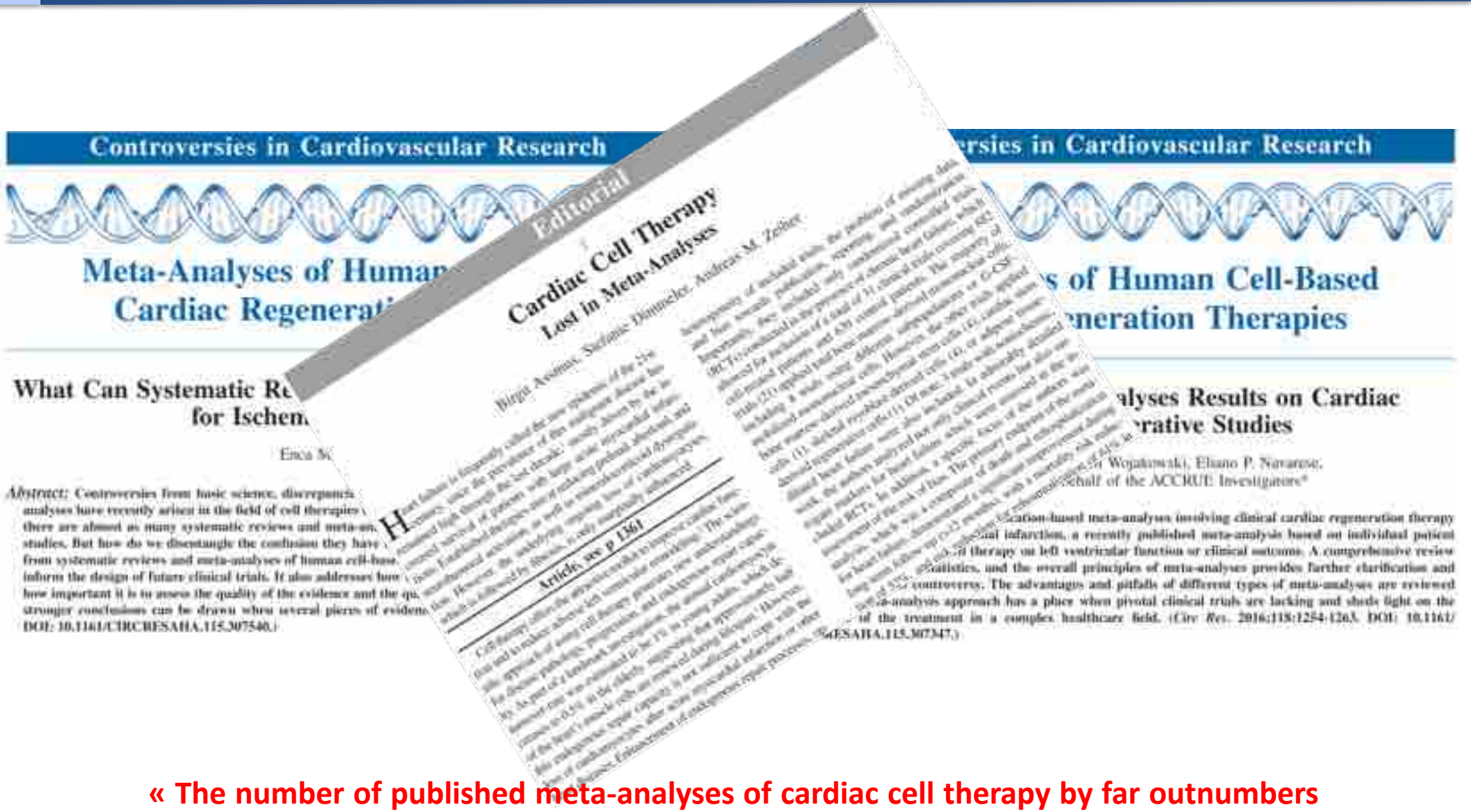
Study or Subgroup	Cell therapy Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Aalst	28.6	52.8	19	17.8	33.8	14	1.5%	10.80 [-18.82, 40.42]
ASTAMI	-11.2	36	50	-1.8	17.6	50	10.8%	-9.40 [-20.51, 1.71]
BONAMI	21.7	31.9	47	20.1	25.6	47	9.7%	1.60 [-10.09, 13.29]
BOOST	7.6	19.9	30	3.4	11.1	30	20.0%	4.20 [-3.95, 12.35]
CADUCEUS	-5.7	51.3	17	-1.1	24.3	8	1.5%	-4.60 [-34.23, 25.03]
FINCELL	6.5	37.9	34	6.3	34.4	36	4.6%	0.20 [-16.79, 17.19]
LATE-TIME	5	33.2	55	3.7	35.9	26	5.0%	1.30 [-15.05, 17.65]
REGENT	4.1	33.4	90	-0.3	22.2	32	12.5%	4.40 [-5.92, 14.73]
REPAIR-AMI	12.1	30.5	95	14.1	31.5	92	16.9%	-2.00 [-10.89, 6.89]
SCAMI	98.3	48	22	76.7	39.8	12	1.5%	21.60 [-8.56, 51.76]
SWISS-AMI	20.6	33.9	107	27.1	38.6	60	9.8%	-6.50 [-18.19, 5.19]
TIME	24.9	39	75	22.4	36.4	37	6.2%	2.50 [-12.18, 17.18]
Total (95% CI)			**641**			**444**	**100.0%**	**0.20 [-3.45, 3.85]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.62$, df = 11 (P = 0.66); $I^2 = 0\%$
Test for overall effect: Z = 0.11 (P = 0.91)

Changes in End-diastolic Volume (ml)
Mean Difference IV, Random, 95% CI
-50 -25 0 25 50
Favours Cell therapy Favours Control

Gyöngyösi M et al, Circ Res, 2015

Thérapies cellulaires – méta-analyses, Infarctus



« The number of published meta-analyses of cardiac cell therapy by far outnumbers the number of well controlled randomized trials » Assmus B, Circ Res, 2015

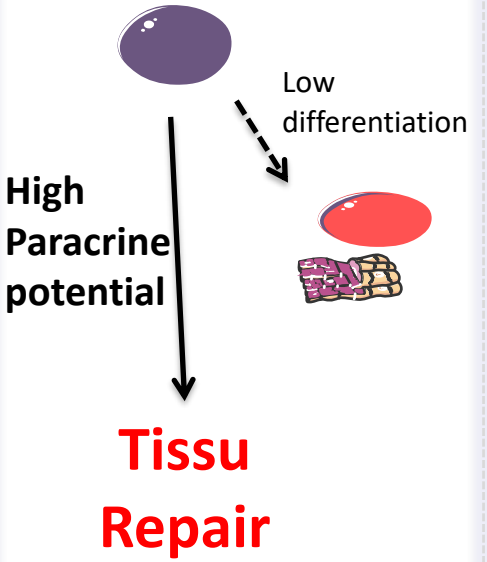
4- Leçons des stratégies de thérapie cellulaire

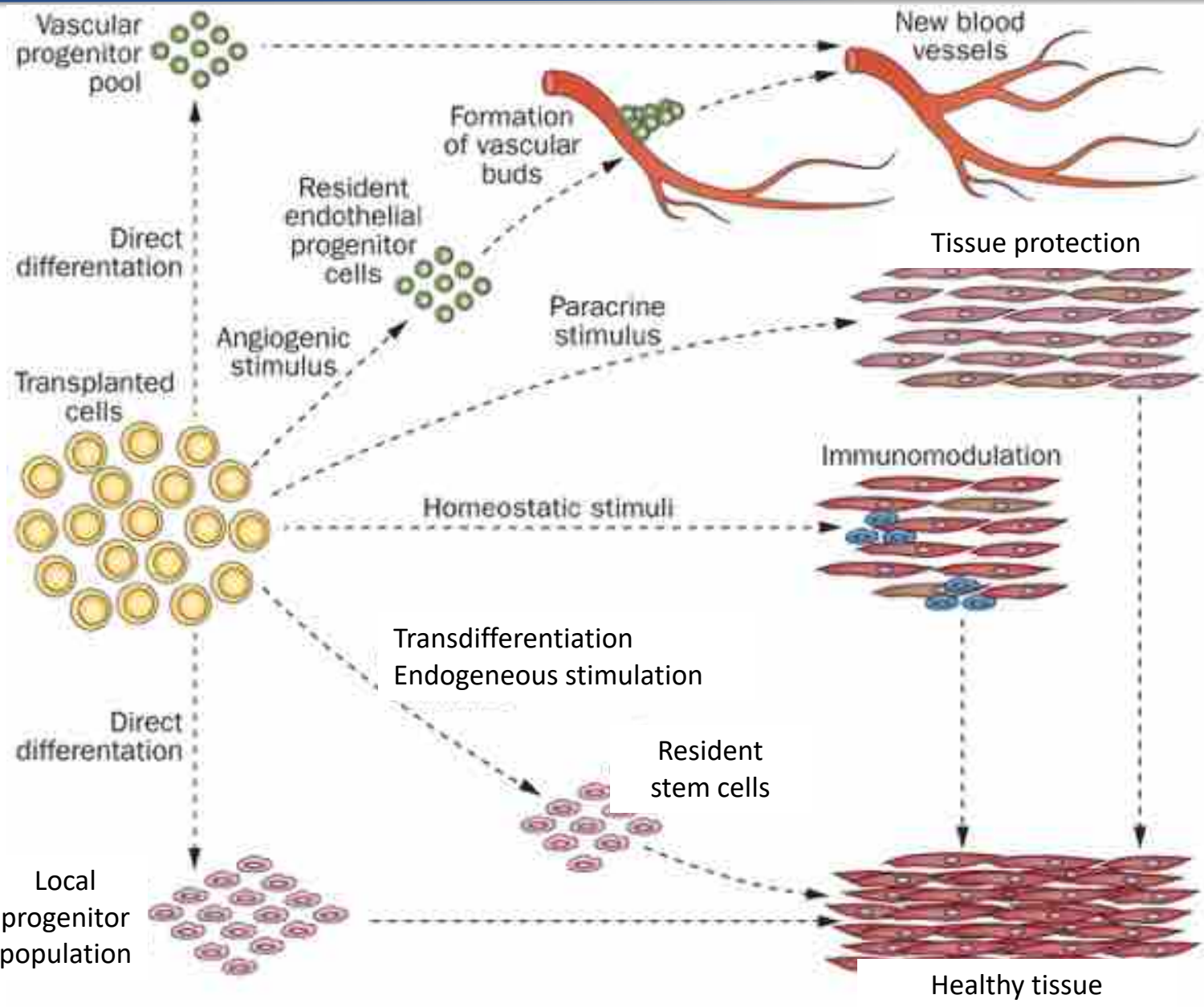
Essais cliniques - Leçons

Type de cellules?
Doses?
Timing des injections?
Site d'injection?
Groupes contrôles?
Critères d'efficacité?
Nombre de patients?

Leçon 1: Effets pléiotropiques et paracrines

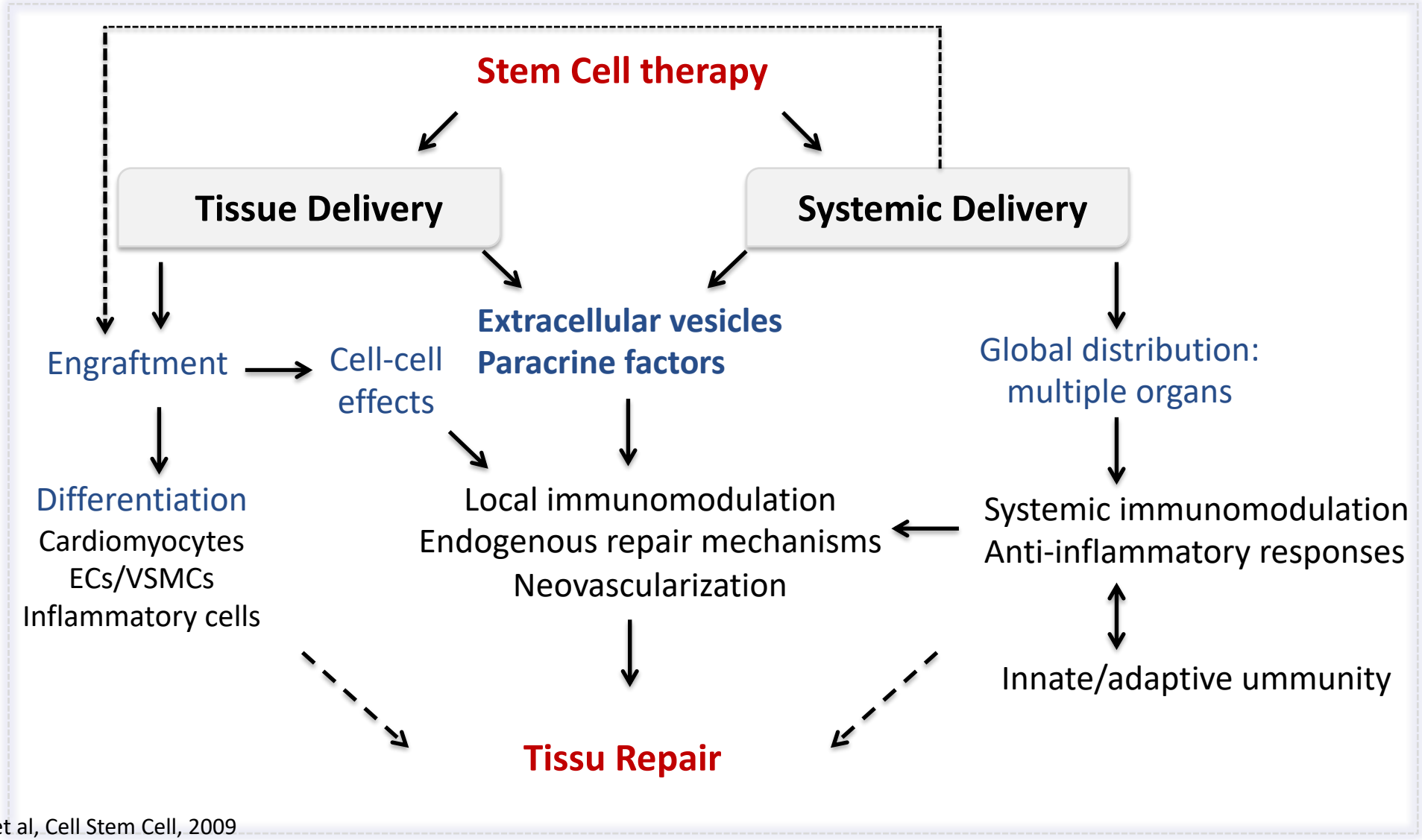
When less is more: Paracrine effect





Adapted from Behfar, A et al, Nat. Rev. Cardiol, 2014

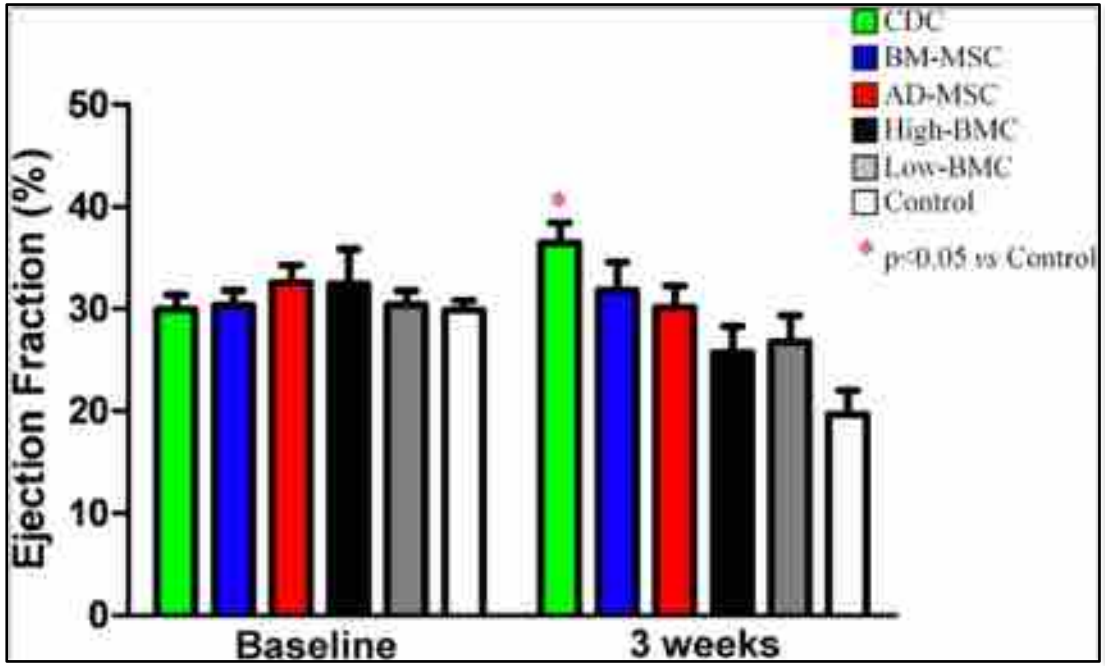
Leçon 2: Effets locaux et systémiques



Lee RH, et al, Cell Stem Cell, 2009
Luger D et al, Circ Res, 2017
Hamid T et al, Circ Res, 2017

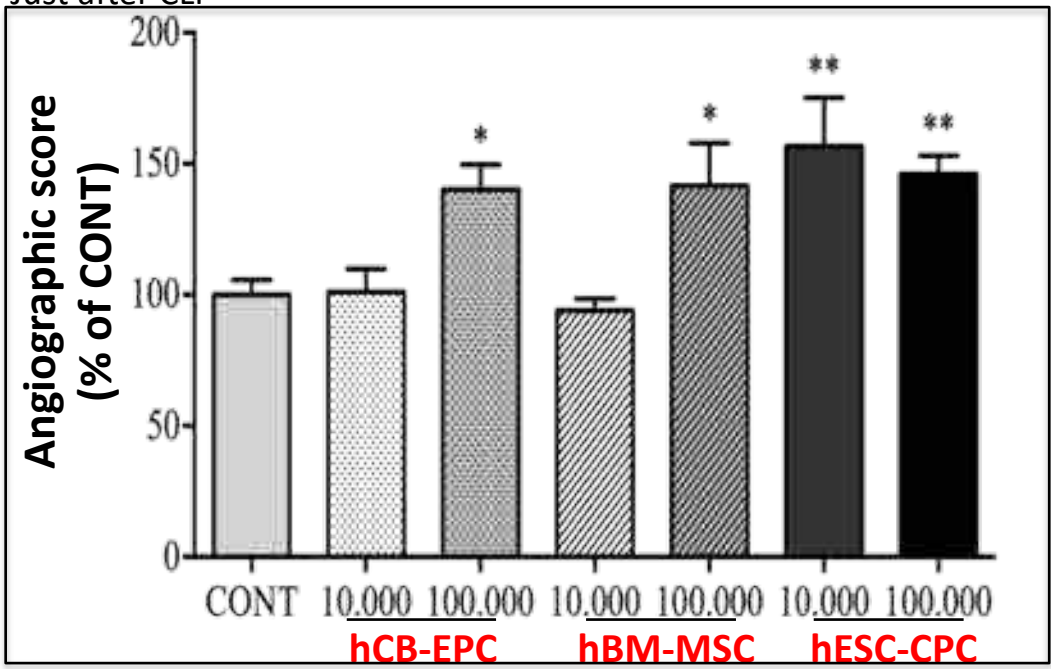
Leçon 3: L'origine des cellules souches thérapeutiques compte!

Intracardiac injection
Just after MI



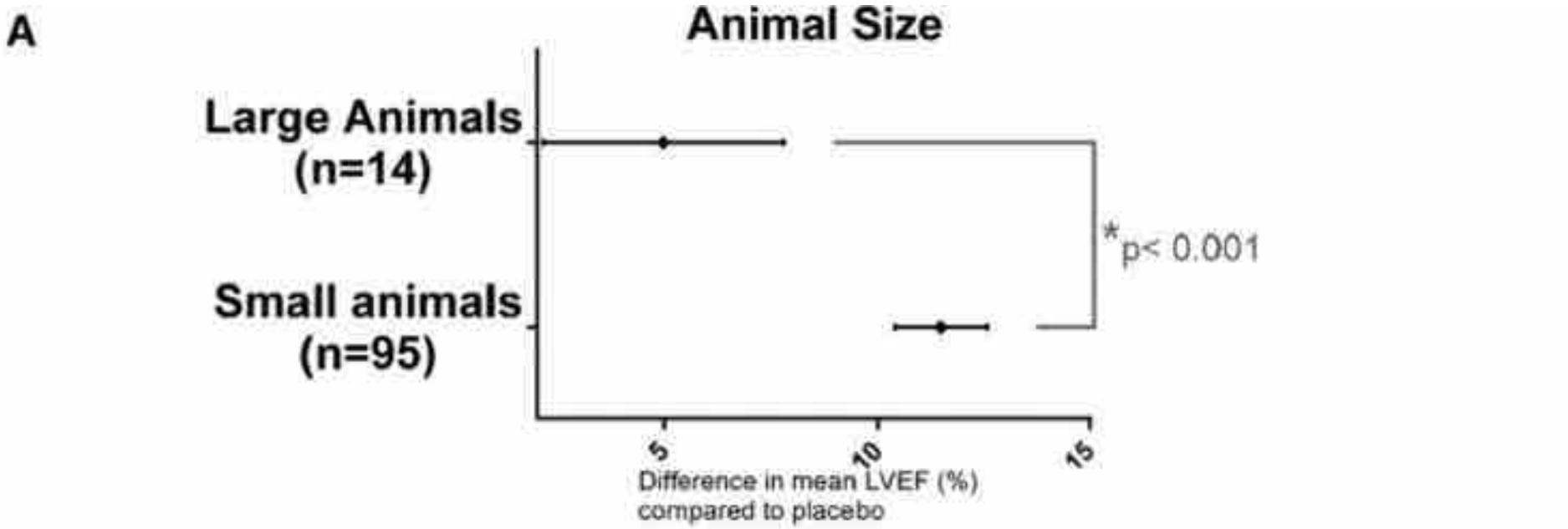
Li TS et al, J Am Coll Cardiol, 2012

Intramuscular injection
Just after CLI



Richart A et al, Stem Cells, 2014

Difference between small and large animal studies.



CDC cardiosphere-derived cells & Cs, cardiospheres.

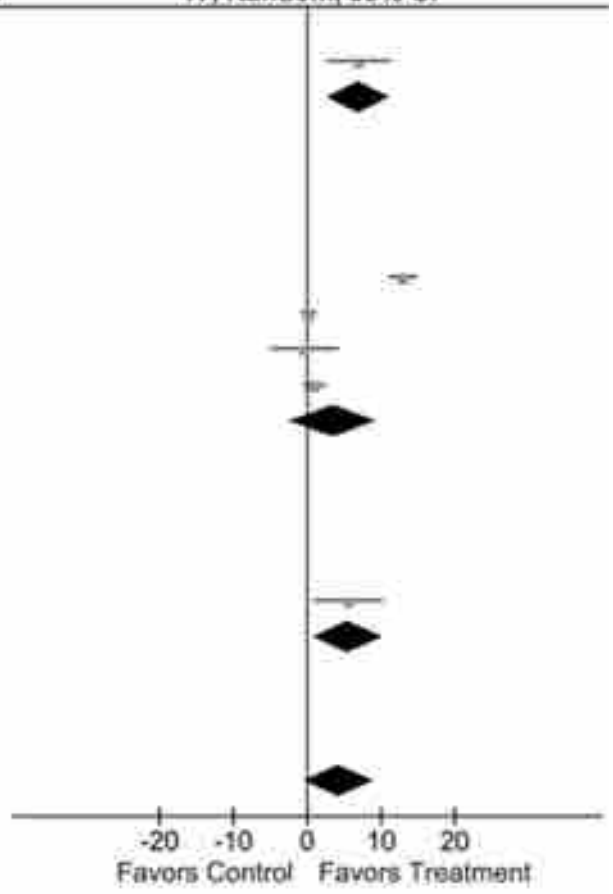
Type de cellules?, Doses?, Timing des injections?, Site d'injection?
Groupes contrôles, Critères d'efficacité, Nombre de patients?

Zwetsloot et al, Circ Res, 2016

Leçon 4: Design de l'approche thérapeutique: Site d'injection ?

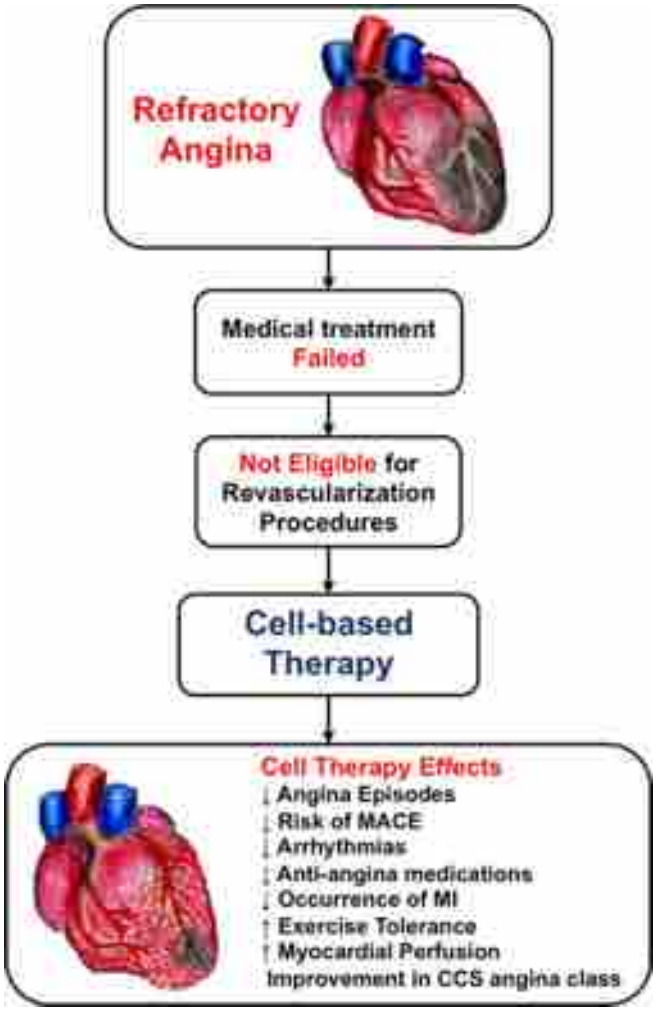
End point: left ventricular ejection fraction (LVEF; %) in acute myocardial infarction (AMI) clinical trials. Result favors transendocardial stem cell injection (TESI) and intravenous infusion (IV). MSC-based therapy.

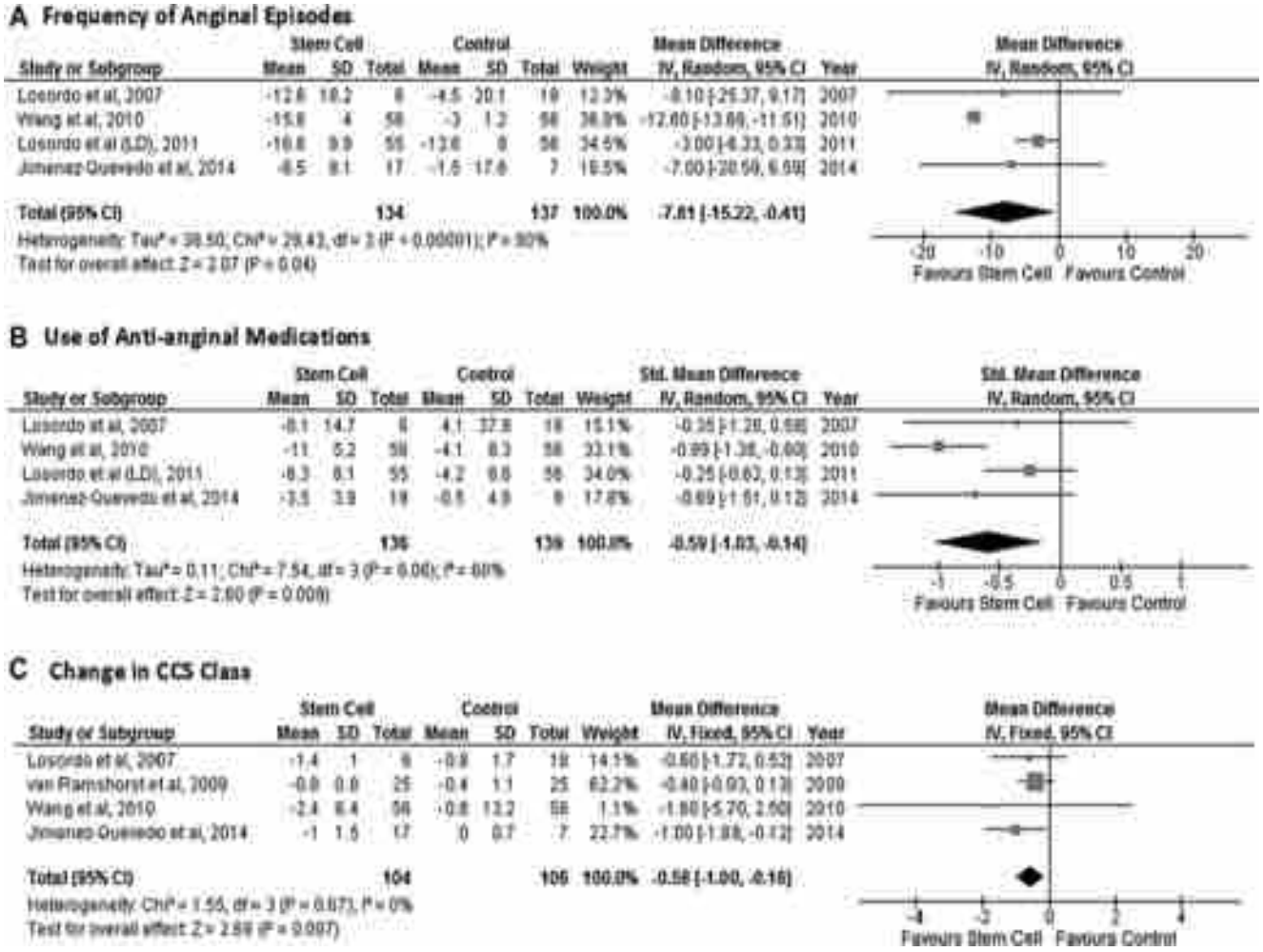
Study or Subgroup	Treatment Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
TESI								
Rodrigo et al. 2013	57	3	8	50	12	38	15.7%	7.00 [2.66, 11.34]
Subtotal (95% CI)			**8**			**38**	**15.7%**	**7.00 [2.66, 11.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.16 (P = 0.002)								
Intracoronary Infusion								
Chen et al. 2004	67	3	34	54	5	35	17.6%	13.00 [11.06, 14.94]
Gao et al. 2013	55.1	1.9	21	54.9	1.7	22	18.0%	0.20 [-0.88, 1.28]
Lee et al. 2014	50	8.4	30	50.4	9.4	28	15.5%	-0.40 [-5.00, 4.20]
Wang et al. 2014	50.1	3.4	28	49.1	2.3	30	17.8%	1.00 [-0.50, 2.50]
Subtotal (95% CI)			**113**			**115**	**68.9%**	**3.54 [-2.39, 9.46]**
Heterogeneity: $Tau^2 = 34.80$; $Chi^2 = 135.40$, df = 3 (P < 0.00001); $I^2 = 98\%$								
Test for overall effect: Z = 1.17 (P = 0.24)								
Intravenous Infusion								
Hare et al. 2009	52.5	11.87	39	46.9	6.87	21	15.3%	5.60 [0.86, 10.34]
Subtotal (95% CI)			**39**			**21**	**15.3%**	**5.60 [0.86, 10.34]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.31 (P = 0.02)								
Total (95% CI)			**160**			**174**	**100.0%**	**4.40 [-0.29, 9.10]**
Heterogeneity: $Tau^2 = 31.55$; $Chi^2 = 140.82$, df = 5 (P < 0.00001); $I^2 = 96\%$								
Test for overall effect: Z = 1.84 (P = 0.07)								
Test for subgroup differences: $Chi^2 = 0.86$, df = 2 (P = 0.65), $I^2 = 0\%$								



Kanelidis et al, Circ Res, 2017

Leçon 4: Design de l'approche thérapeutique: Type de patients?



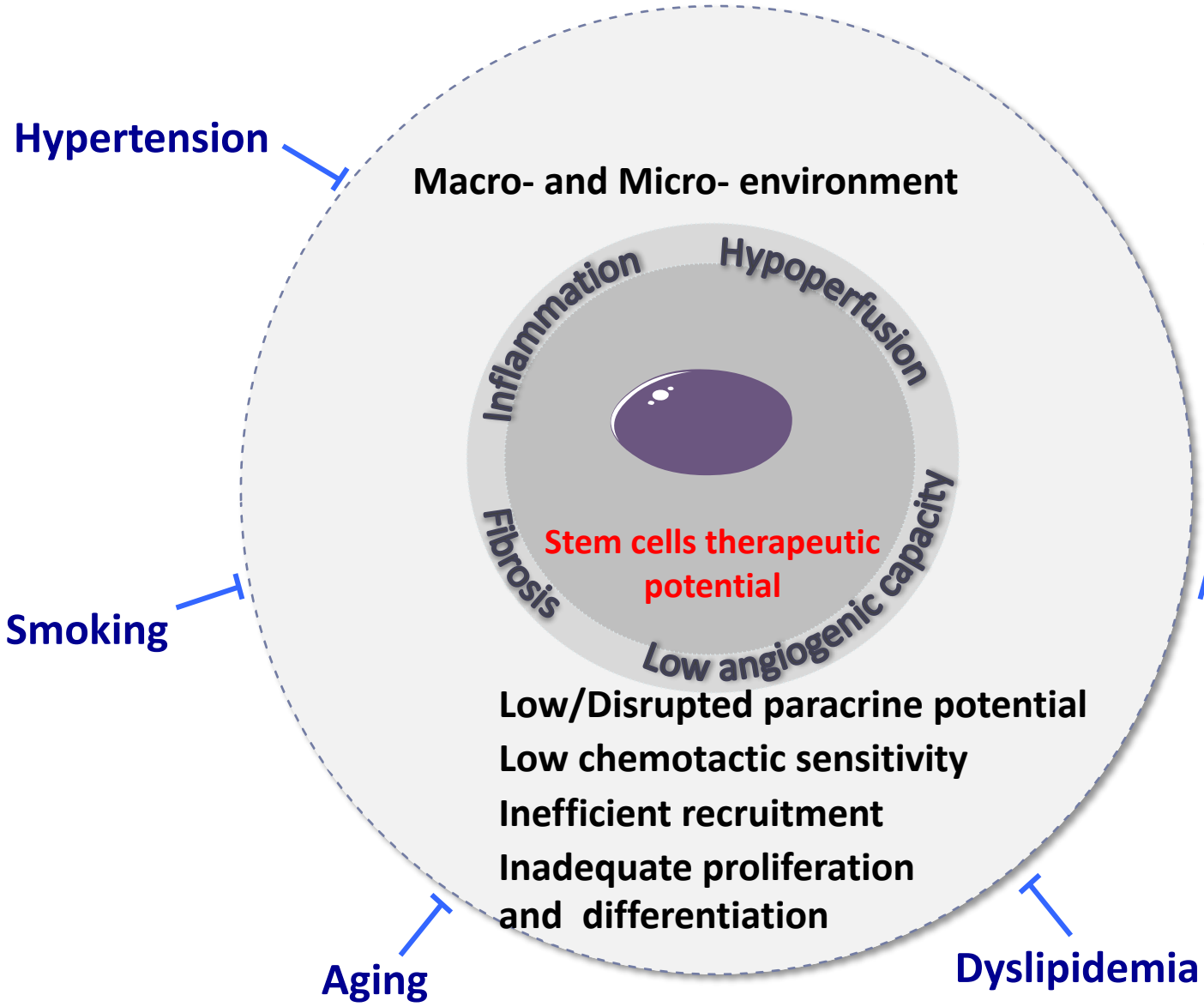


All sources of therapeutic cells

Florea V et al, Circ Res, 2016

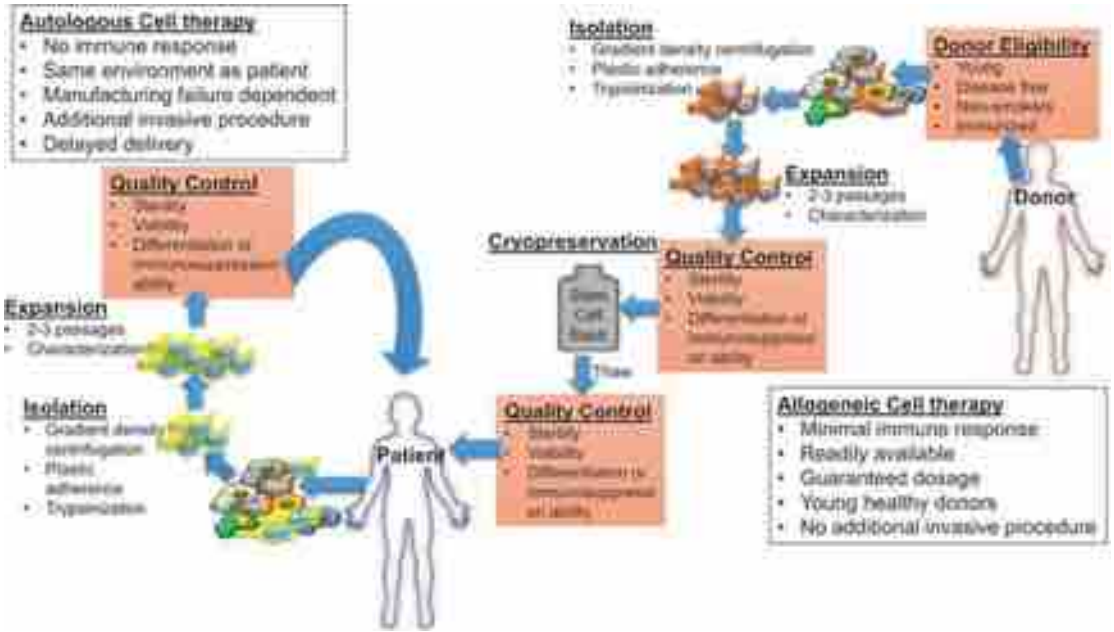
Khan AR et al, Circ Res, 2016

Leçon 5: Faible efficacité des cellules souches adultes



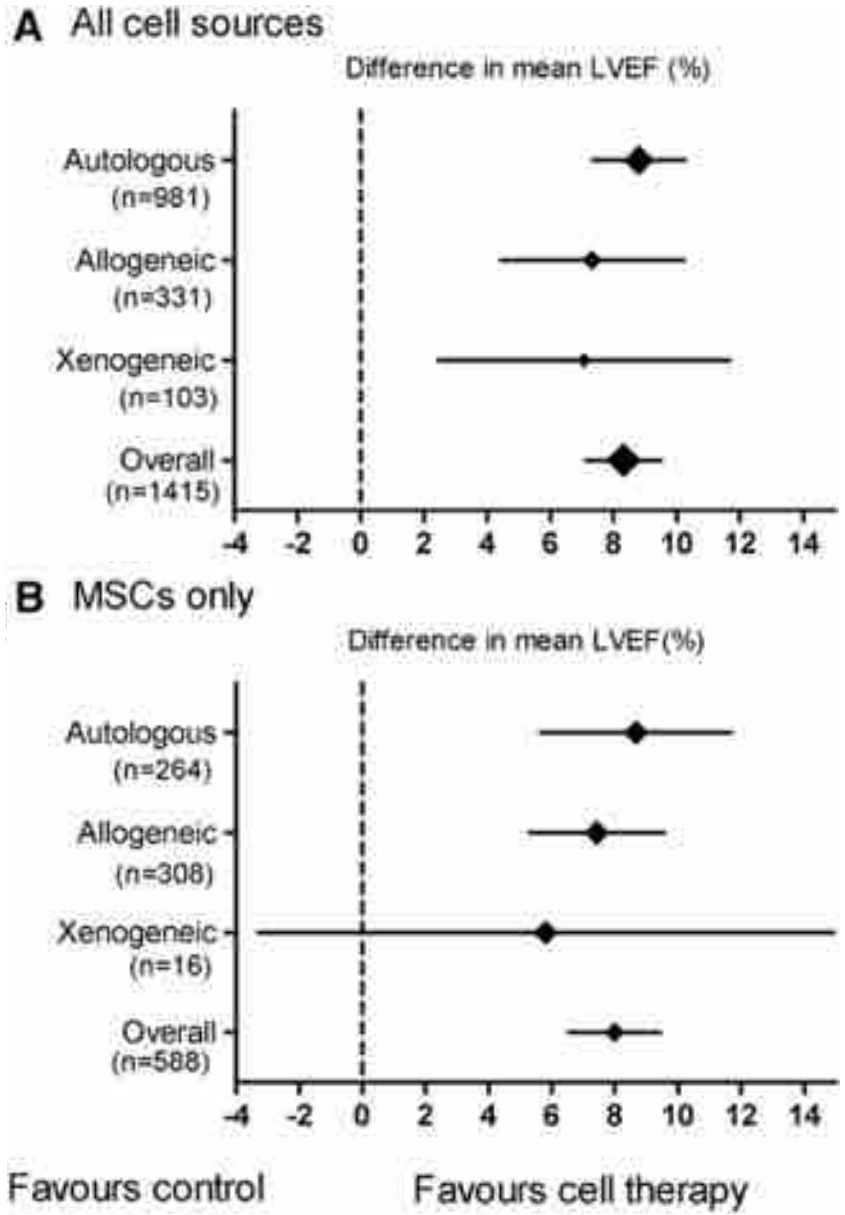
Howangyin K et al, Stem Cells, 2014
Broquères-You D et al, Diabetes, 2012
Mees B et al, Am J Pathol, 2011
Carrière A, Arterioscler Thromb Vasc Biol, 2009
You D et al, Hypertension, 2008
Ebrahimian TG et al, Am J Pathol, 2006
You D et al, Circulation, 2006
Tamarat R et al, Am J Pathol, 2004
Planat-Benard V/Silvestre JS et al, Circulation, 2004
Silvestre JS et al, Circulation, 2003

Leçon 5: Faible efficacité des cellules souches adultes



Systematic literature search to identify publications describing controlled preclinical trials of unmodified stem cell therapy in large animal models of myocardial ischemia.

Data from 82 studies involving 1415 animals.



Lorkeers S et al, Circ Res, 2015
Karantalis V et al, Circ Res, 2015

5- Stratégies pour augmenter l'efficacité des cellules souches adultes

Adult Stem cells

Bone Marrow

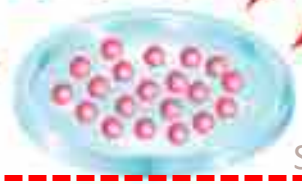
Blood

Skeletal muscle

Adipose tissue

Other sources

Heart



Lineage Selection

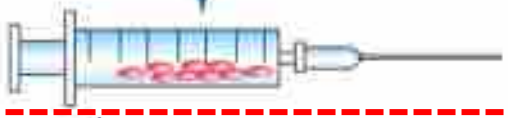
Small molecules

Genes

miR or antagomiR

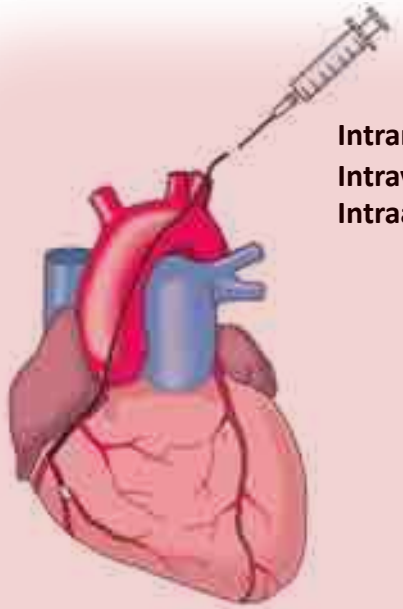
eNOS
VEGF
Ang-1
CCL12
Thrombin

Ephrin B2FC
E selectin
HMBG1
B2 integrin
Statines



Bi-therapy

Biomaterials



Intramuscular
Intravenous
Intraarterial

Treatment of ischemic tissue
Growth Factors
Cytokines

Intramuscular
Intravenous
Intraarterial

Adapted from
Silvestre JS et al, Physiol Rev, 2013

5- Stratégies pour augmenter l'efficacité des cellules souches adultes

Cellules souches mésenchymateuses du sang de cordon
Injection intraveineuse

Clinical Track

OPEN

Safety and Efficacy of the Intravenous Infusion of Umbilical Cord Mesenchymal Stem Cells in Patients With Heart Failure

A Phase 1/2 Randomized Controlled Trial (RIMECARD Trial [Randomized Clinical Trial of Intravenous Infusion Umbilical Cord Mesenchymal Stem Cells on Cardiopathy])

Jorge Bartolucci, Fernando J. Verdugo,* Paz L. González,* Ricardo E. Larrea, Ema Abarzua, Carlos Gouri, Pamela Rojo, Ivan Palma, Ruben Lamich, Pablo A. Pedreros, Gloria Valdivia, Valentina M. Lopez, Carolina Nazzal, Francisco Alcayaga-Miranda, Jimena Cuenca, Matthew J. Brobeck, Amit N. Patel, Fernando E. Figueroa,† Marwan Khoury†

Rationale: Umbilical cord–derived mesenchymal stem cells (UC-MSC) are easily accessible and expanded in vitro, possess distinct properties, and improve myocardial remodeling and function in experimental models of cardiovascular disease. Although bone marrow–derived mesenchymal stem cells have been previously assessed for their therapeutic potential in individuals with heart failure and reduced ejection fraction, no clinical trial has evaluated intravenous infusion of UC-MSCs in these patients.

Objective: Evaluate the safety and efficacy of the intravenous infusion of UC-MSC in patients with chronic stable heart failure and reduced ejection fraction.

Methods and Results: Patients with heart failure and reduced ejection fraction under optimal medical treatment were randomized to intravenous infusion of allogenic UC-MSCs (Cellistem, Cells for Cells S.A., Santiago, Chile; 1×10⁸ cells/kg) or placebo (n=15 per group). UC-MSCs in vitro, compared with bone marrow–derived mesenchymal stem cells, displayed a 85-fold increase in the expression of hepatocyte growth factor, known to be involved in myogenesis, cell migration, and immunoregulation. UC-MSC–treated patients presented no adverse events related to the cell infusion, and none of the patients tested at 0, 15, and 90 days presented alloantibodies to the UC-MSCs (n=7). Only the UC-MSC–treated group exhibited significant improvements in left ventricular ejection fraction at 3, 6, and 12 months of follow-up assessed both through transthoracic echocardiography ($P=0.0167$ versus baseline) and cardiac MRI ($P=0.025$ versus baseline). Echocardiographic left ventricular ejection fraction change from baseline to month 12 differed significantly between groups (+7.07±6.22% versus +1.85±5.60%; $P=0.028$). In addition, at all follow-up time points, UC-MSC–treated patients displayed improvements of New York Heart Association functional class ($P=0.0167$ versus baseline) and Minnesota Living with Heart Failure Questionnaire ($P<0.05$ versus baseline). At study completion, groups did not differ in mortality, heart failure admissions, arrhythmias, or incident malignancy.

Conclusions: Intravenous infusion of UC-MSC was safe in this group of patients with stable heart failure and reduced ejection fraction under optimal medical treatment. Improvements in left ventricular function, functional status, and quality of life were observed in patients treated with UC-MSCs.

Clinical Trial Registration: URL: https://www.clinicaltrials.gov/ct2/show/NCT01739777. Unique identifier: NCT01739777 (*Circ Res.* 2017;121:1192-1204. DOI: 10.1161/CIRCRESAHA.117.310712.)

Bartolucci J et al, Circ Res, 2017

BMMNC tested for predefined markers that have proangiogenic and cardioreparative potential: Cell Potency Assay (CPA) score (% of CD34+)

Transendocardial injections of BM MNC in the peri-infarct myocardial segments.

Contents lists available at ScienceDirect

American Heart Journal

AHJ

Trial Design

The CardiAMP Heart Failure trial: A randomized controlled pivotal trial of high-dose autologous bone marrow mononuclear cells using the CardiAMP cell therapy system in patients with post-myocardial infarction heart failure: Trial rationale and study design

Amish N. Raval, MD[a,*], Thomas D. Cook, PhD[b], Henricus J. Duckers, MD, PhD[c], Peter V. Johnston, MD[d], Jay H. Traverse, MD[e], William T. Abraham, MD[f], Peter A. Altman, PhD[g], Carl J. Pepine, MD[h]

ARTICLE INFO

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Accepted 14 March 2018

ABSTRACT

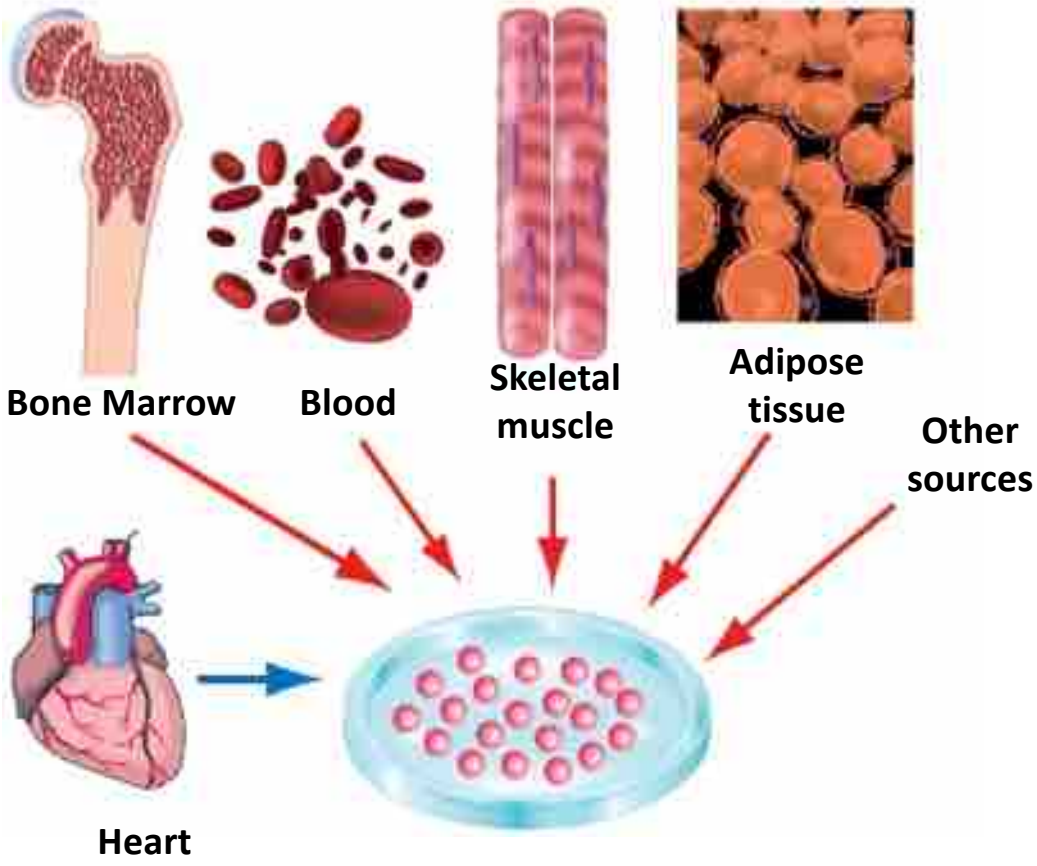
Background: Heart failure following myocardial infarction is a common, disabling, and deadly condition. Direct injection of autologous bone marrow mononuclear cells into the myocardium may result in improved functional recovery, relieve symptoms, and improve other cardiovascular outcomes.

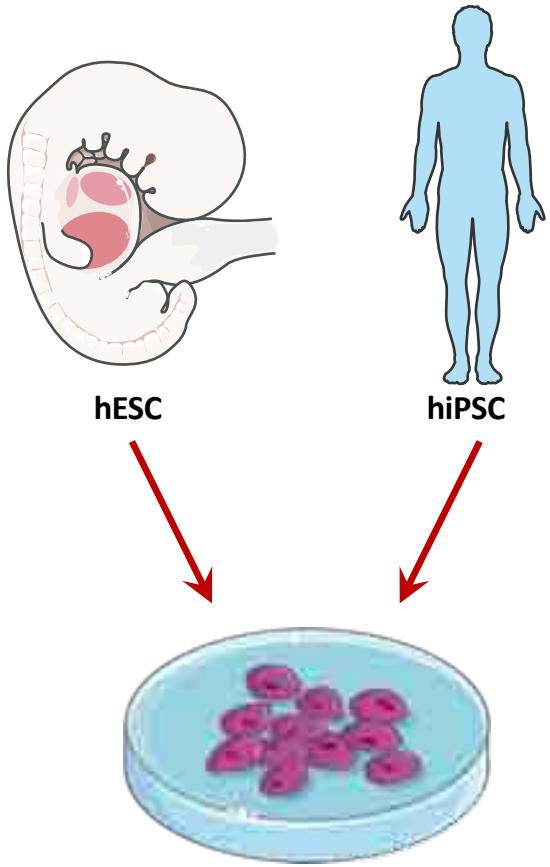
Methods: CardiAMP HF is a randomized, double-blind, sham-controlled, pivotal trial designed to investigate the safety and efficacy of autologous bone marrow mononuclear cells treatment for patients with medically refractory and symptomatic ischemic cardiomyopathy. The primary end point is change in 6-minute walk distance adjusted for major adverse cardiovascular events at 12 months following treatment. Particularly novel aspects of this trial include a cell potency assay to screen subjects who have bone marrow cell characteristics that suggest a favorable response to treatment, a point-of-care intraoperative method, a high target dose of 200 million cells, and an efficient transendocardial intraoperative delivery method that is associated with high cell retention.

Conclusions: This novel approach may lead to a new treatment for those with ischemic heart disease suffering from medically refractory heart failure.

Raval AN et al, Am Heart J, 2018

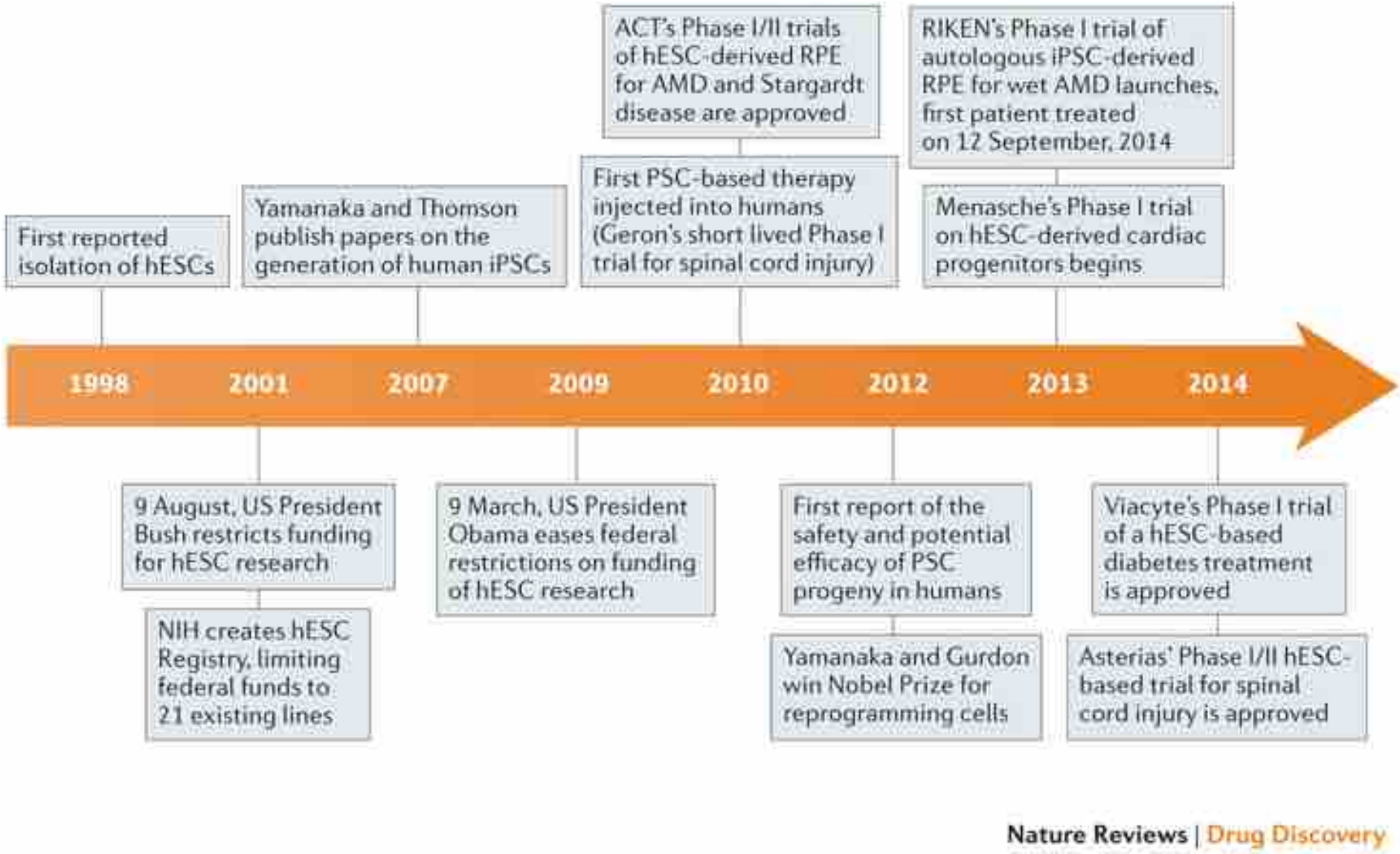
6- Thérapies cellulaires: Utilisation de Cellules souches pluripotentes





Adapted from Silvestre JS et al, Physiol Rev, 2013

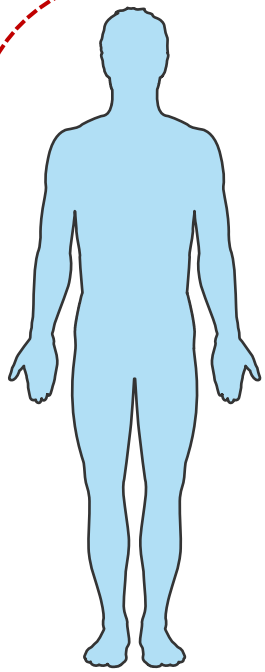
Dates principales dans le développement des thérapies basées sur l'administration de cellules souches pluripotentes (iPSC & ESC)



Kimbrel EA, Nat Rev Drug Discovery, 2015

6-a Cellules Souches pluripotentes induites (iPSCs)

Generation of iPSC lines



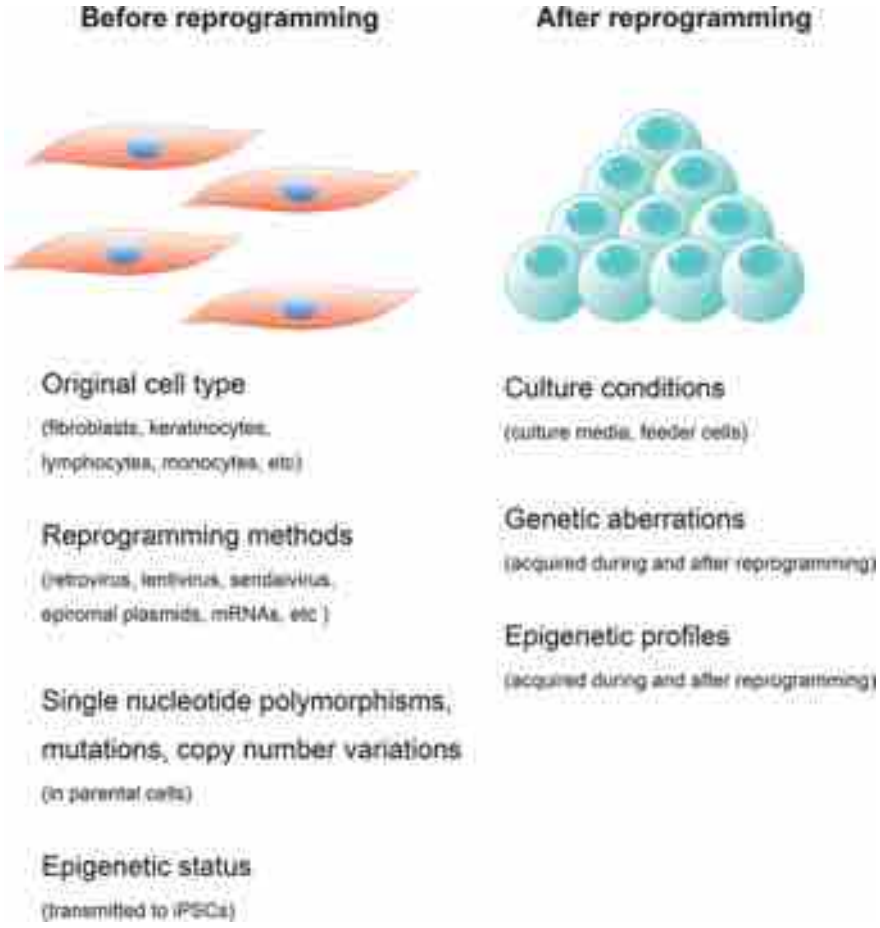
Transcription factors
c-Myc/L-Myc, Oct ¾,
So2, Klf4, Nanog

iPSC

Retrovirus, Lentivirus,
Adenovirus, Plasmid,
chemical compounds,
miRNA etc..

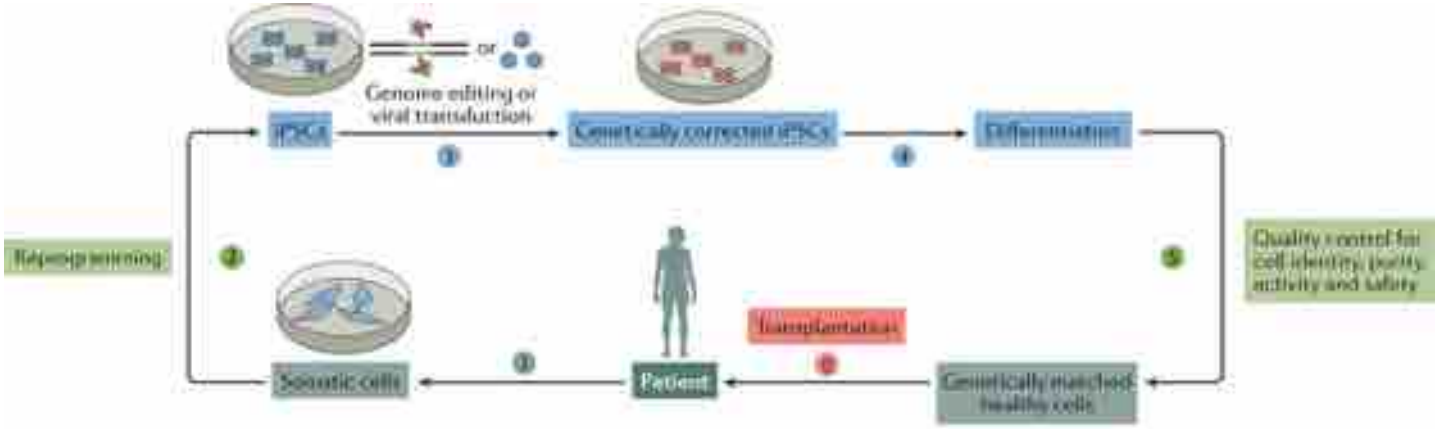
Fibroblats, keratinocytes
Lymphocytes, monocytes Etc..

Clonal differences of iPSC



Yoshida et al, Circ Res, 2017

1- Disease modeling and insights onto new therapies

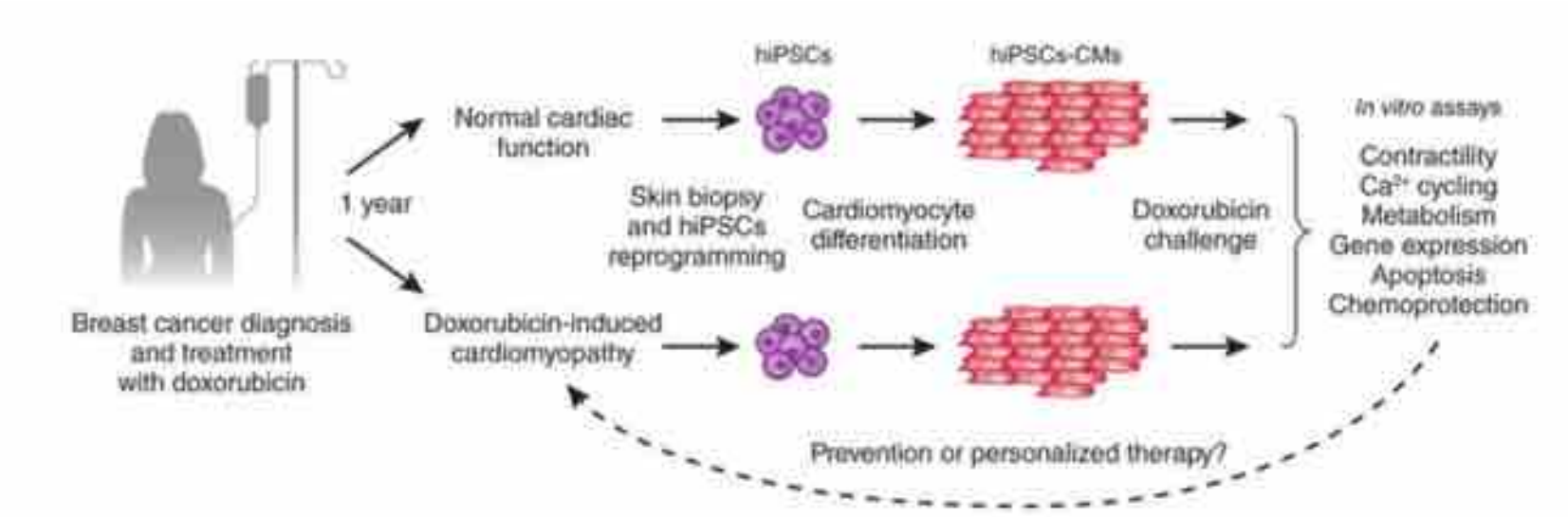


Correction of the *GATA4* G296S point mutation, using the CRISPR/Cas9 gene-editing system, in the patient-specific reprogrammed iPS cells backs to the wild-type (WT) alleles

G296S cardiomyocytes reveal features of cardiomyopathy in vitro, displaying reduction in contractility, sarcomeric disorganization, and impairment in calcium handling and metabolism. The isogenic corrected cells exhibit a normal cardiomyocyte phenotype, proving the function of the mutation.

Ang YS et al, Cell, 2016
Vujic A et al, Cell, 2016
Shi Y et al, Nat Rev Drug Discov, 2017

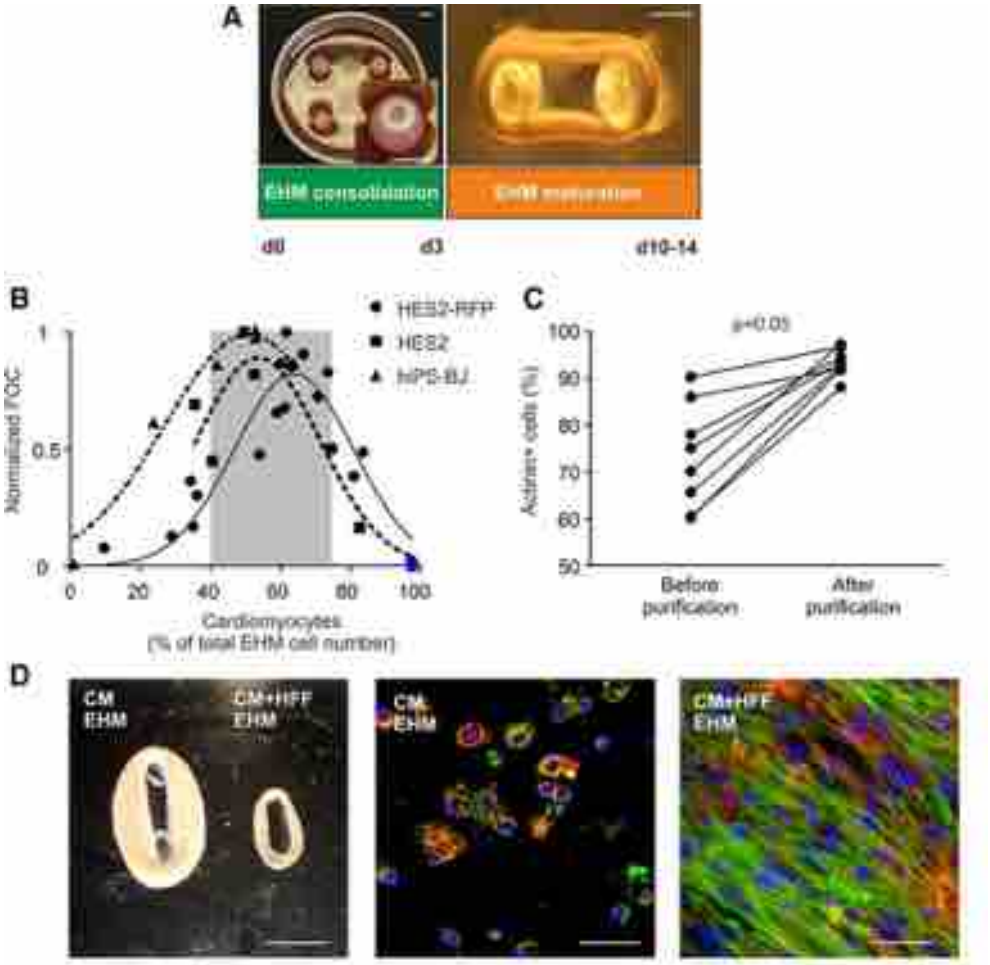
2- Prediction of drug toxicity and/or efficiency



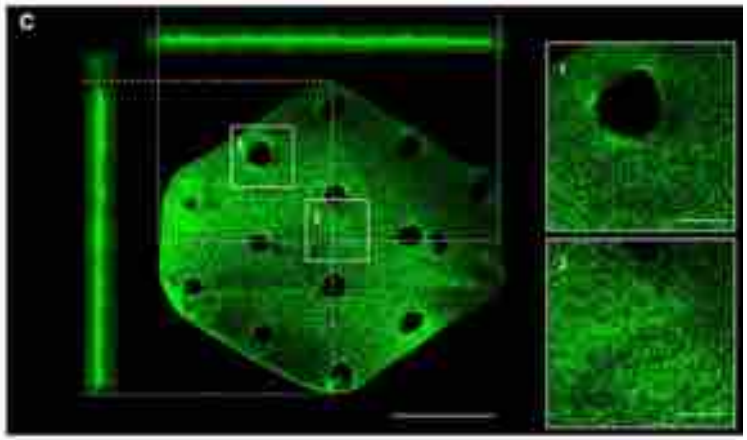
Burridge *et al* derive hiPSCs from skin biopsy of individuals with breast cancer who do and do not experience doxorubicin-induced toxicity. They find that these cells respond differently to doxorubicin. Hence, they can be used to investigate the cause of toxicity and, in the future, potentially to tailor relevant treatments.

Burridge PW et al, Nat Med, 2016
Biermann M et al, Nat Med, 2016

3- Design of engineered myocardium or cardiac muscle patches



Tiburcy et al, Circulation, 2017



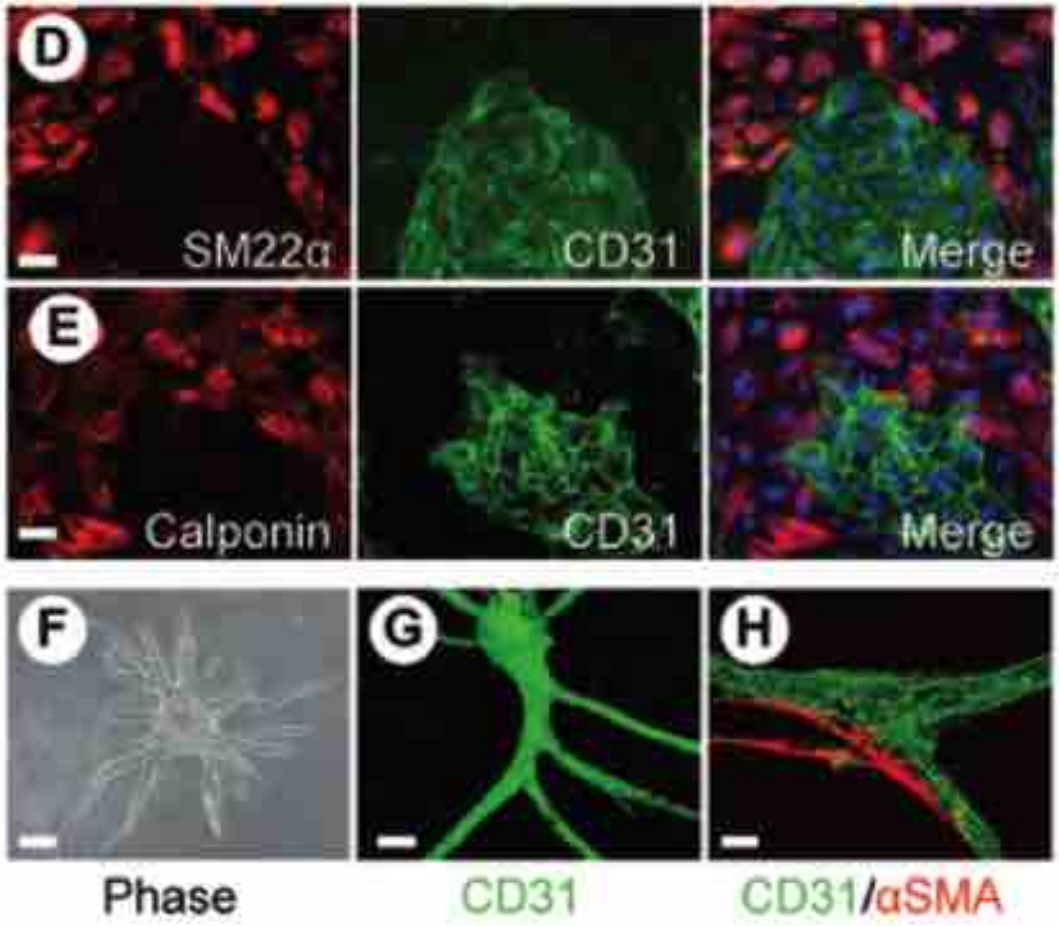
3D fibrin patch
Fibrin scaffold
Multiphoton-excited 3D printing

+ smooth muscle & endothelial cells
+ IGF encapsulated microspheres

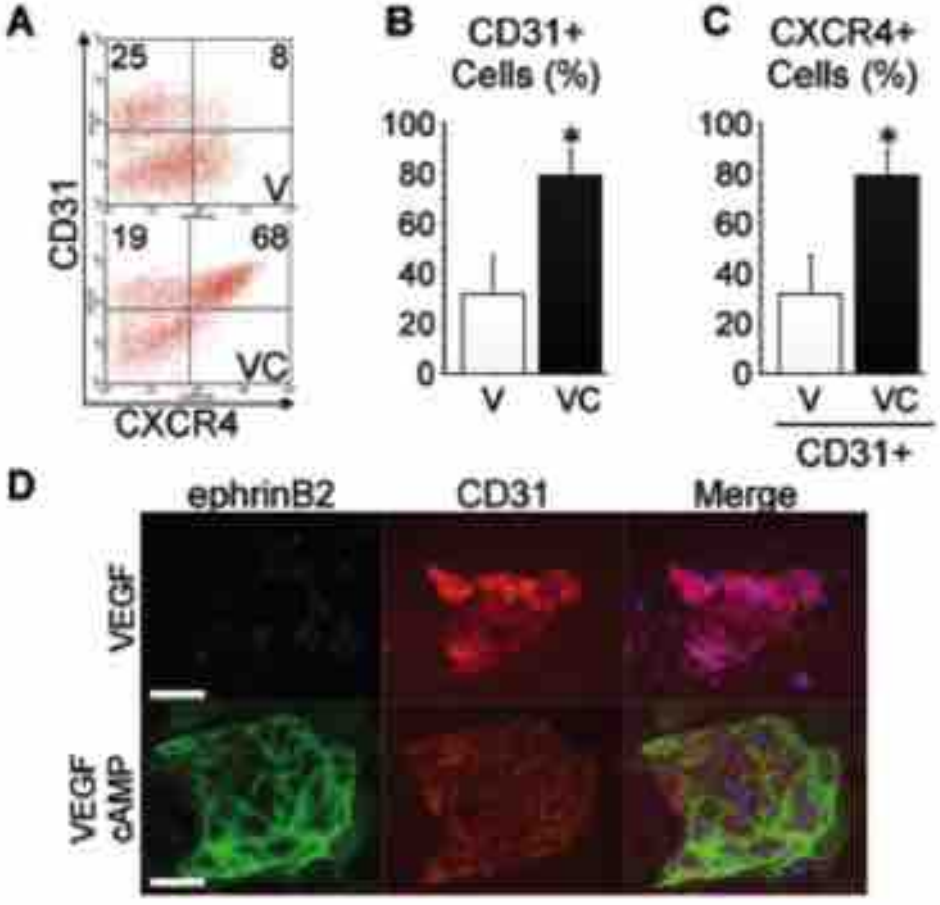
Gaol L et al, Circulation, 2018
Gao L et al, Circ Res, 2017
Ye L et al, Cell Stem Cell, 2014

Cellules souches pluripotentes induites (iPS): preuves expérimentales

√Differentiation of iPS to vascular cells



√Arterial and venous EC induction from iPS cell-derived FLK-1+ cells



Germline-competent mouse Nanog-iPS cell lines 20D17, 38C2 and 38D2

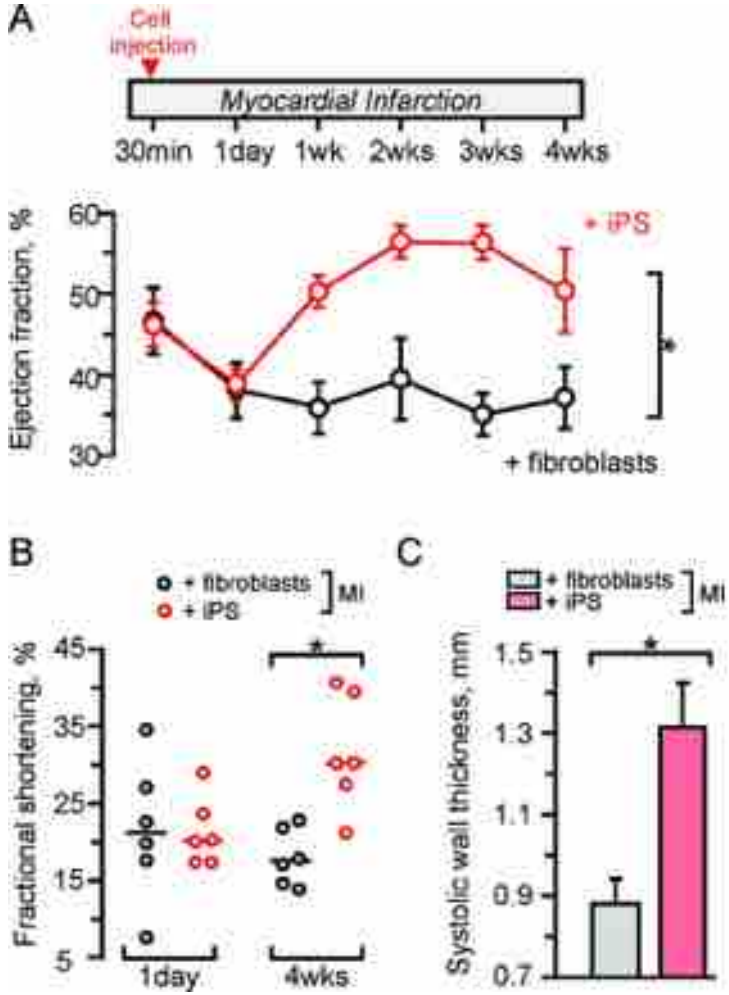
Flk-1 mesoderm cells induced by 96 to 108h culture of iPS

Narazaki G et al, Circulation, 2008

Mauritz C et al, Circulation, 2008

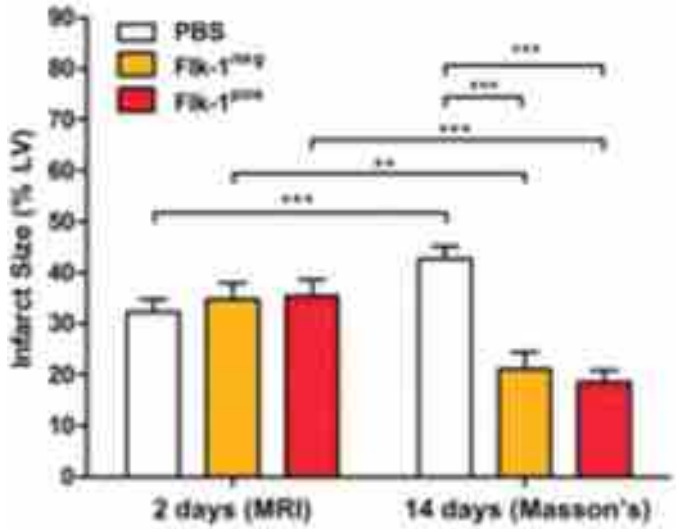
Cellules souches pluripotentes induites (iPS): preuves expérimentales

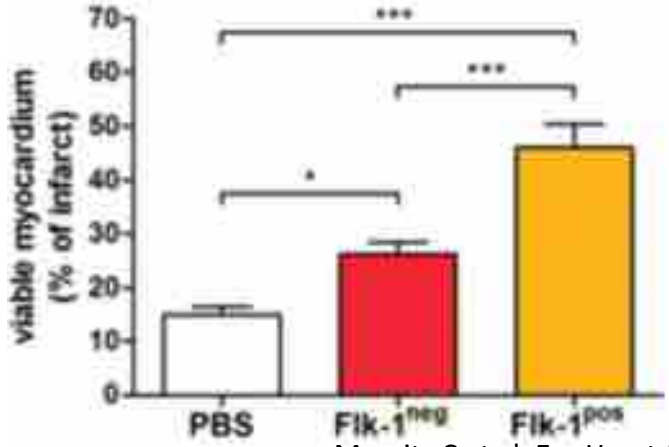
Mouse fibroblasts
Oct3/4, Sox2, Klf4, c-MYC (plasmids)
IC injection 30 min after MI



Nelson TJ et al, Circulation, 2009

Embryonic fibroblasts
Oct3/4, Sox2, Klf4, c-MYC (plasmids)
IC injection after MI





Mauritz C et al, Eur Heart J, 2011

Cellules souches pluripotentes induites (iPS): preuves cliniques

Pilot safety study of iPSC-based intervention for wet-type AMD

› Top | › News | › FAQ | › Media contact

About AMD | Pilot study | For patients

Pilot safety study of iPSC-based intervention for wet-type AMD

This site provides an introduction to a pilot safety study on the transplantation of autologous induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) cell sheets in patients with exudative (wet-type) age-related macular degeneration (AMD). Use the links above to read more about the disease, the research plan, and other information for patients, or click the image to the right for a TTS-friendly single-page version of the site.

Summary
Single-page version of the site for a TTS-friendly

News

Oct.9.2015
Update on first transplant recipient

Sep.11.2015
On the enrollment of patients in the clinical study

Sep.12.2014
On the first transplant case

Sep.17.2013

Contact

Foundation for Biomedical Research and Innovation
IBRI Hospital
saisei@fbri.org
IBRI Hospital
Department of Ophthalmology
2-2 Minatojima-minamimachi, Chuo-ku, Kobe 6500047, Japan

RIKEN

Foundation for Biomedical Research and Innovation

New Scientist

34

THIS WEEK 8 August 2015

Mutation alert halts stem cell trial to cure blindness

A PIONEERING stem-cell trial has been halted after genetic mutations were discovered in the cells of a participant. One of the mutations may carry a remote risk of cancer.

The trial is the first to explore whether cells known as induced pluripotent stem (iPS) cells can be used to treat disease. These are made by taking cells from someone's skin and using a cocktail of chemicals to "rewind" them to a stem-cell-like state. This means they have the potential to turn into almost any other type of cell, allowing them to be converted into the type required, before being transplanted back.

In this trial, skin cells were turned into retinal cells in an attempt to reverse the damage to eyes caused by age-related macular degeneration, which leads to loss of vision and can cause blindness. The first patient, a 70-year-old woman, was treated last September and is reportedly in good health.

There is a lot resting on the outcome of the trial. It could finally provide evidence of the clinical potential of iPS cells, which were first created in 2006.

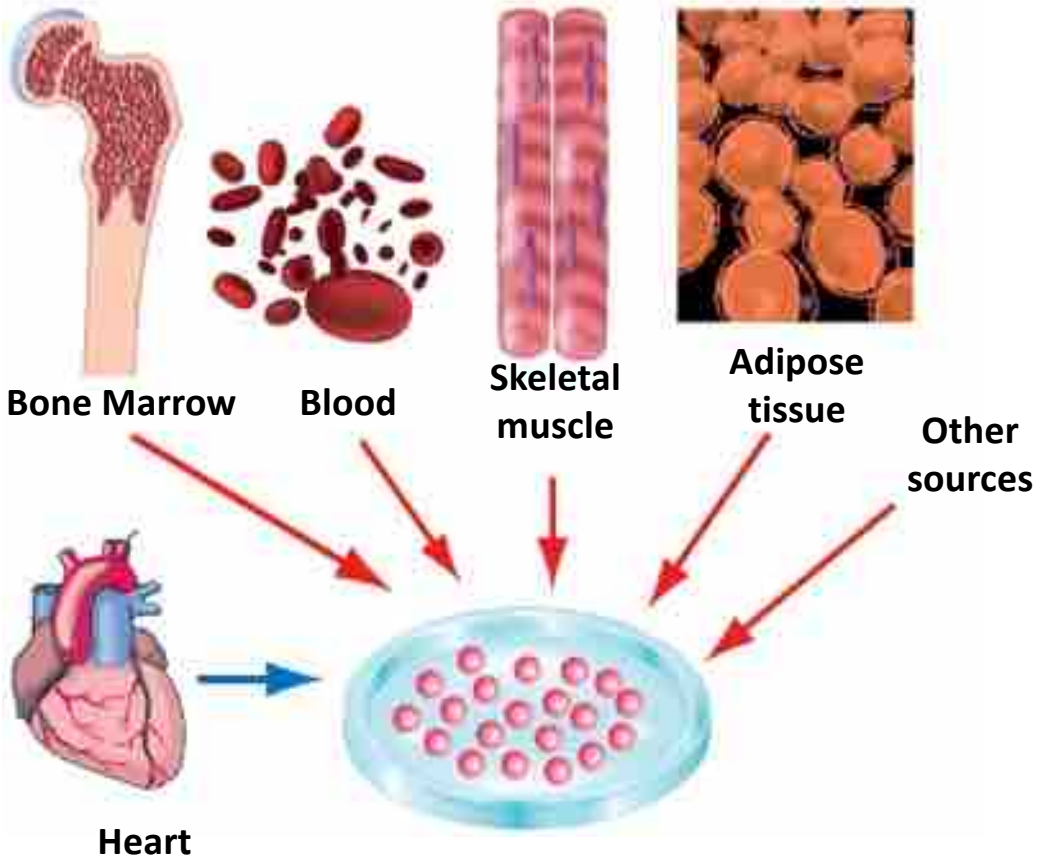
"A mutation was found in the cells before transplantation into the second patient, and this is something we took into account when we made the decision to suspend the study for the time being," says trial leader Masayo Takahashi of the Riken Centre for Developmental Biology in Kobe, Japan.

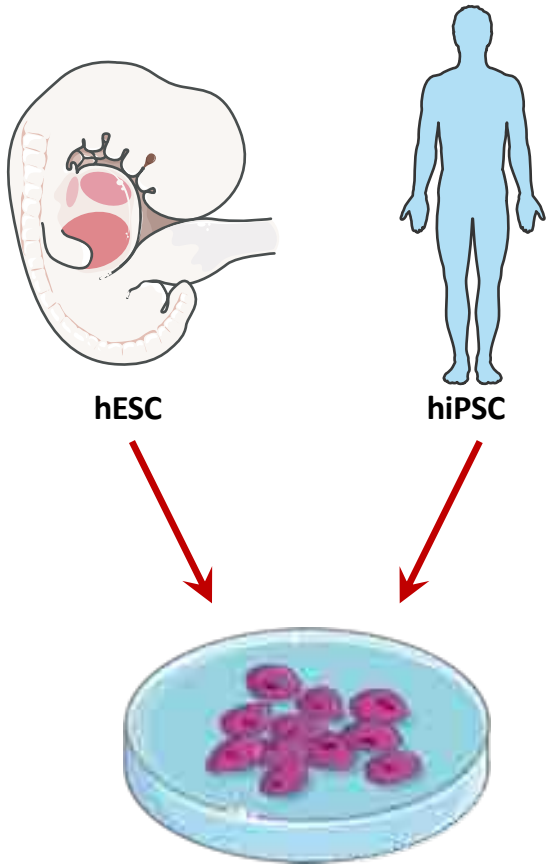
Analysis of the patient's cells revealed six mutations. Three were genes that had been deleted and three were changes to genes, including one in an oncogene – a gene with the potential to cause cancer, although this one is linked with a low risk. The mutations were not detectable in the original skin cells, suggesting that they occurred as a result of the iPS-cell procedure.

"Either they were there at undetectable

New Scientist;8/8/2015, Vol. 227 Issue 3033, p9

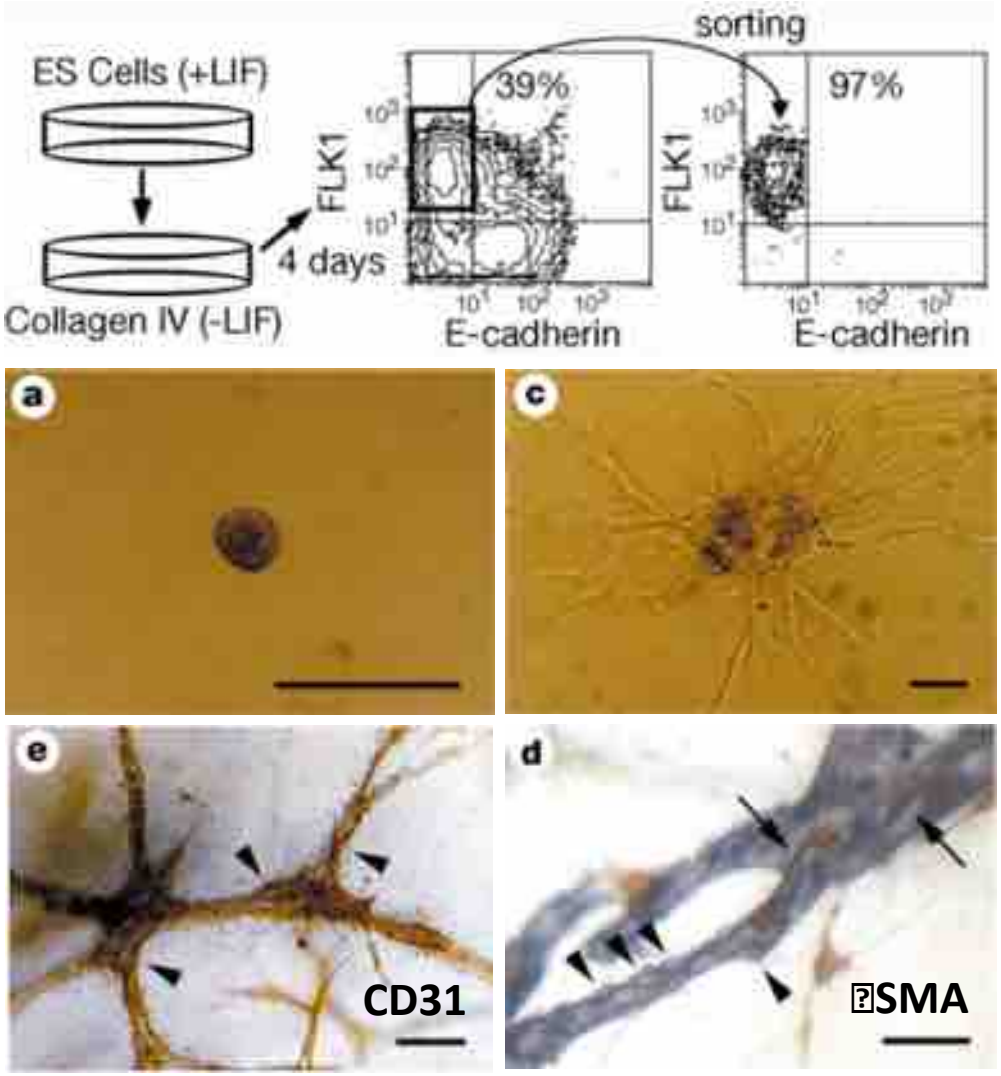
6-b Thérapies cellulaires: Cellules souches pluripotentes embryonnaires

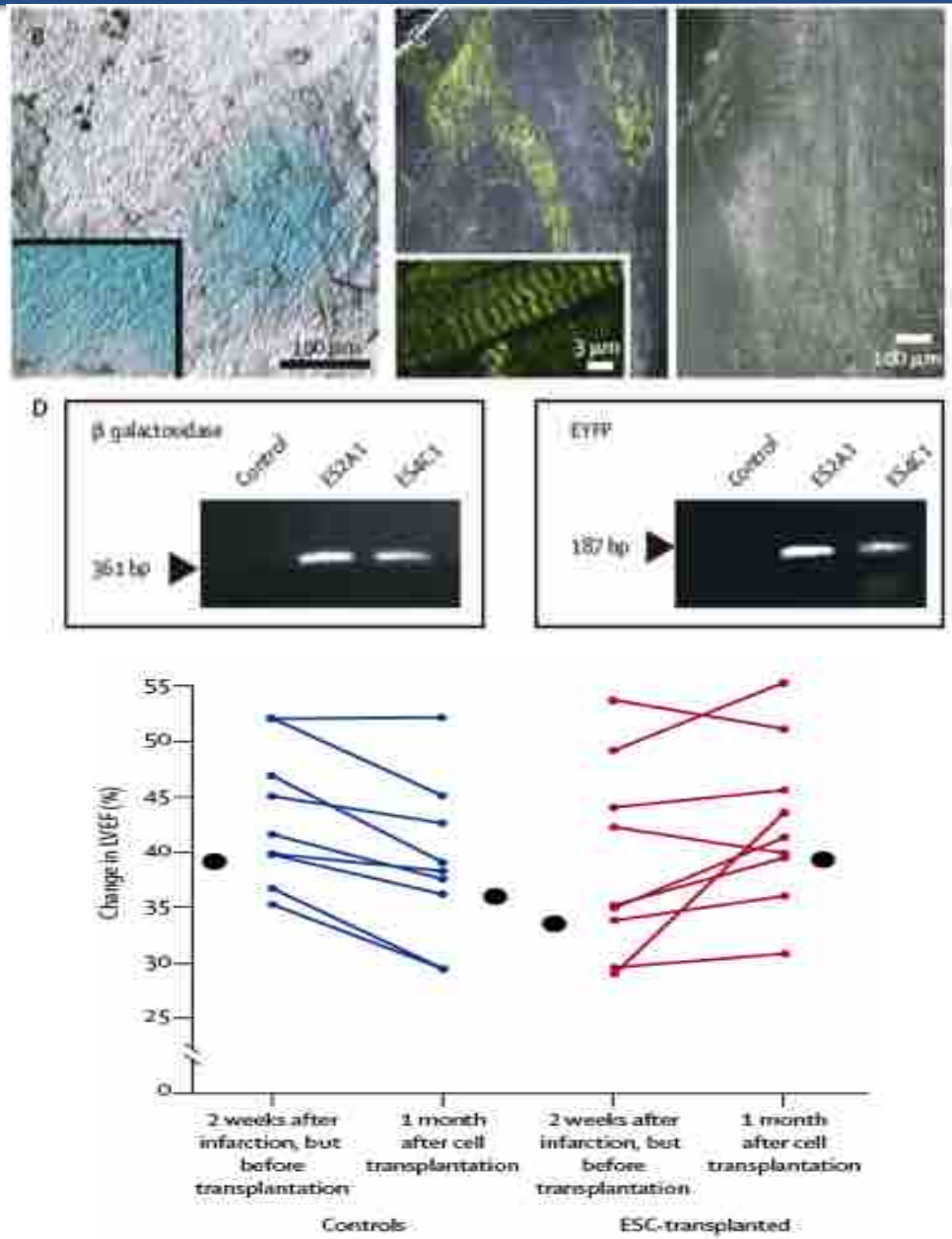




Adapted from Silvestre JS et al, Physiol Rev, 2013

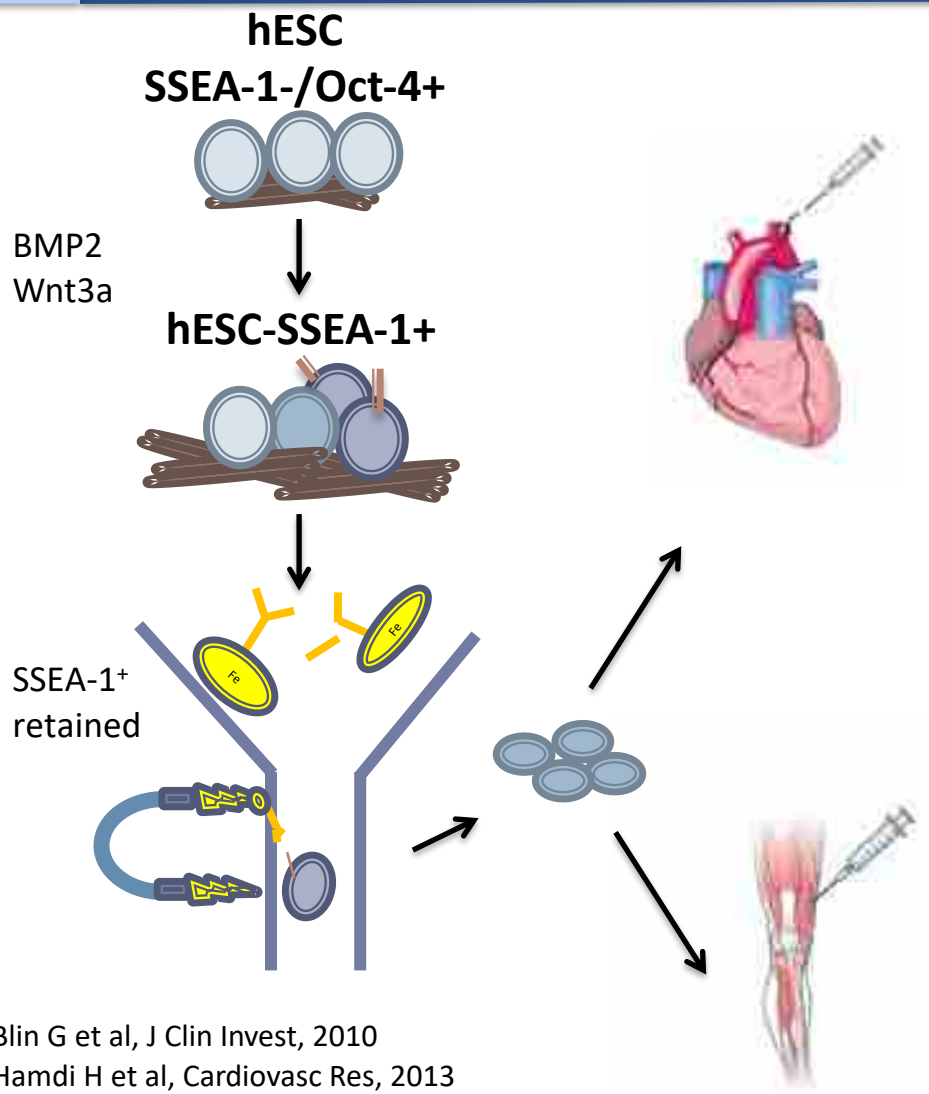
Cellules souches pluripotentes embryonnaires: preuves expérimentales





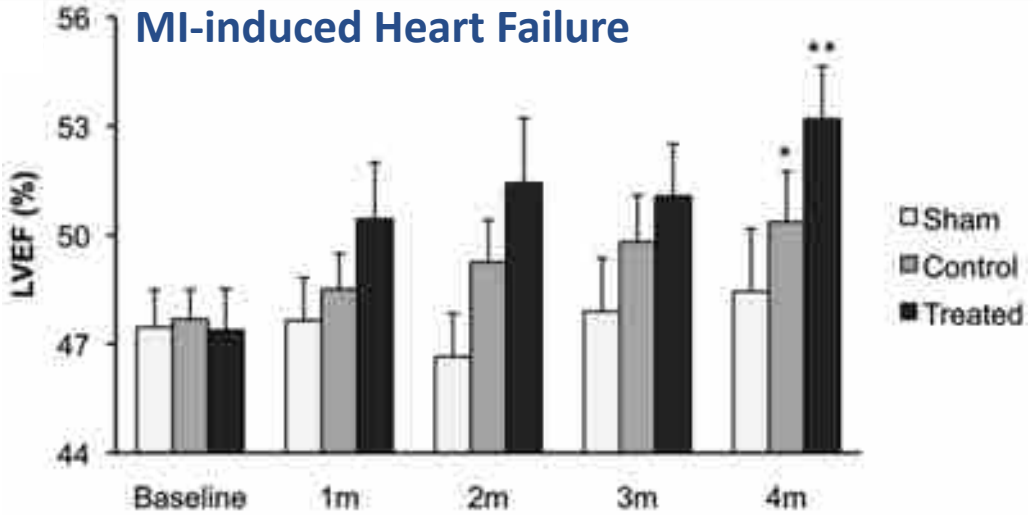
Yamashita J et al, Nature, 2000
Menard C et al, Lancet, 2005

Cellules souches pluripotentes embryonnaires: preuves expérimentales

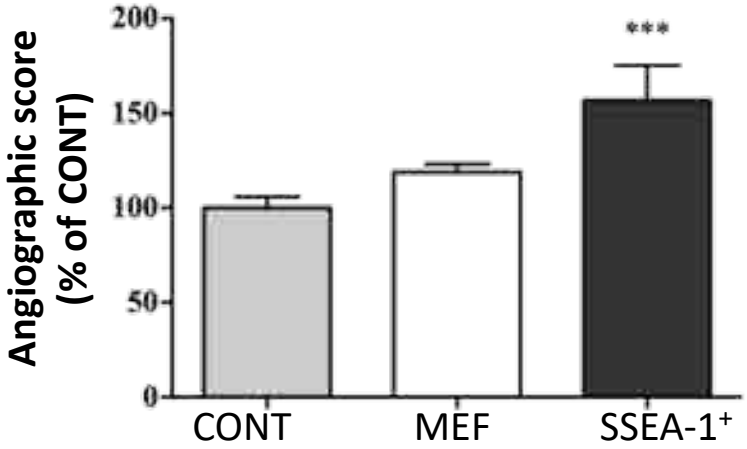


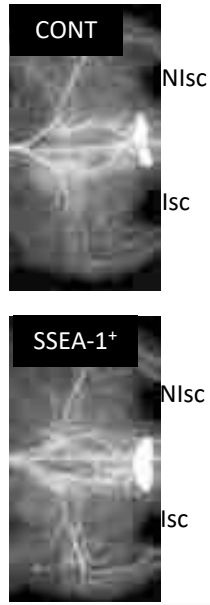
Blin G et al, J Clin Invest, 2010
Hamdi H et al, Cardiovasc Res, 2013
Richart A et al, Stem Cells, 2014
Menasché P et al, Eur Heart J, 2015
Bellamy V et al, J Heart Lung Transplant, 2015
Menasché P et al, J Am Coll Cardiol, 2018

MI-induced Heart Failure



Limb Ischemia





Cellules souches embryonnaires: preuves cliniques

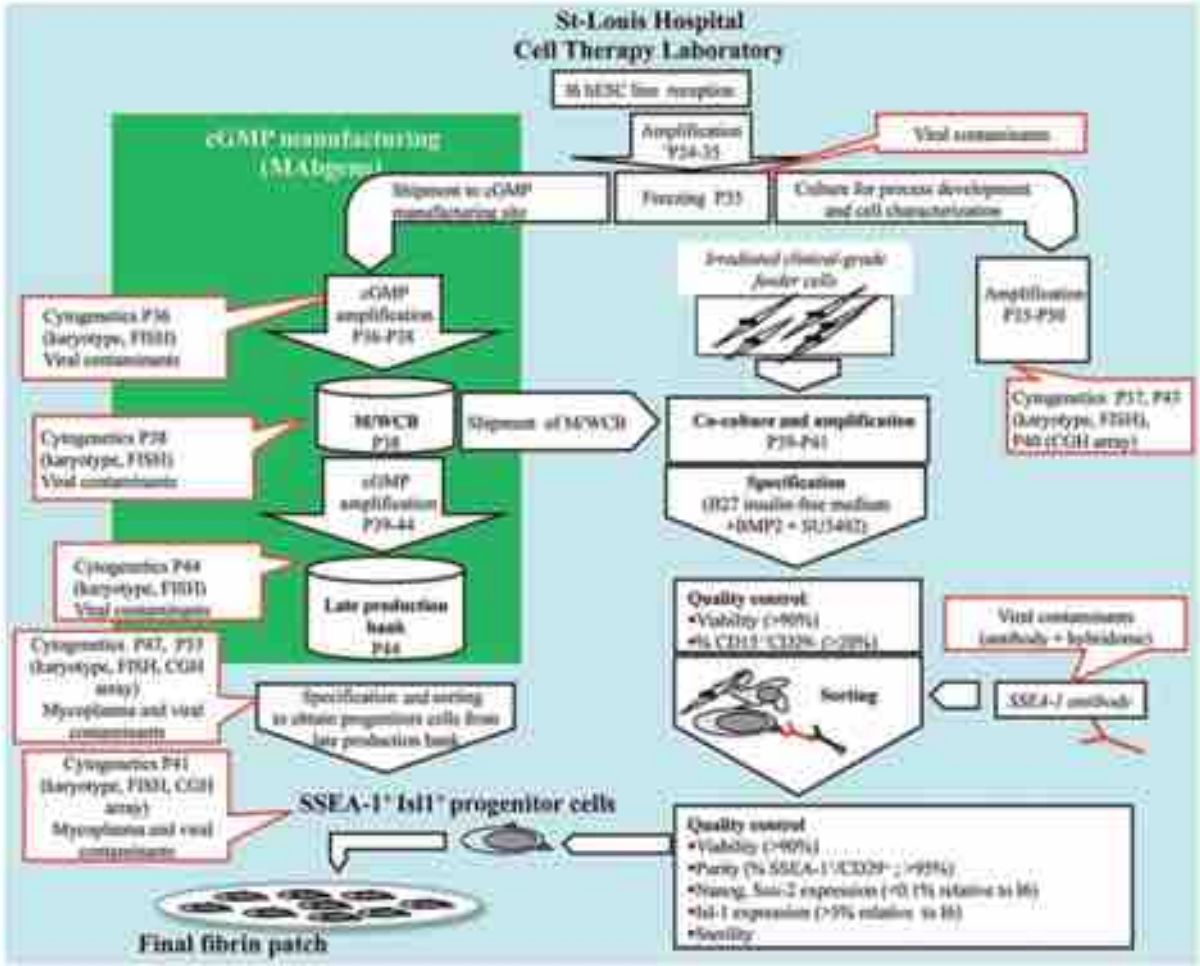
ESCORT Trial

- 6 patients with severe LV dysfunction (EF ≤ 35%)
- SSEA-1$^+$ *Isl*-1$^+$ cardiac progenitors embedded in a surgically delivered fibrin patch

- Outcome measures:

✓ Feasibility : Scale-up, cardiac specification, purification:
Established

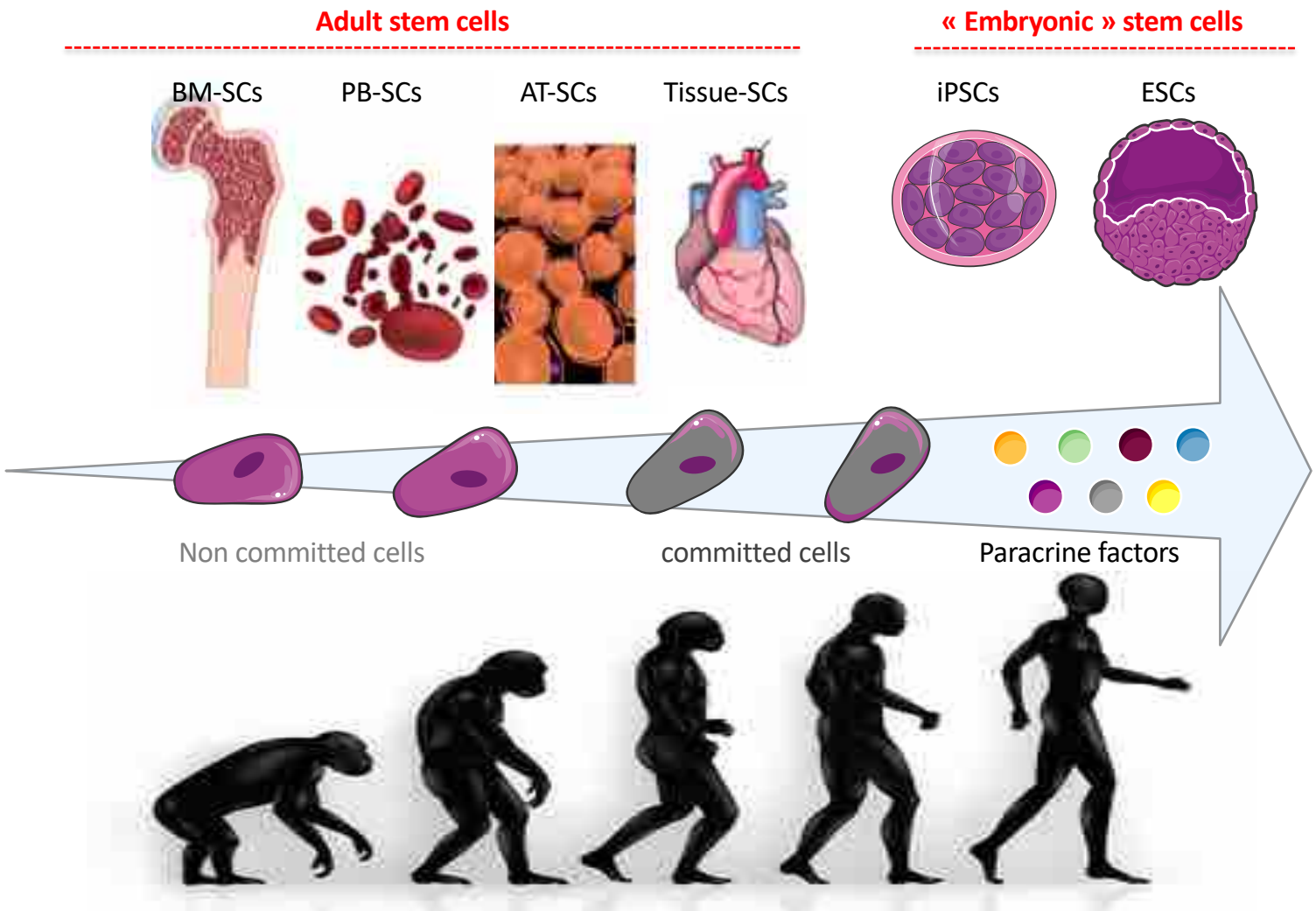
✓ Safety: Arrhythmias (ICD recordings) & tumor (whole-body CT scans and PET-scans)
No safety issues (FU 3 mo. - 2.5 years)



Menasché P et al, Eur Heart J, 2015
Bellamy V et al, J Heart Lung Transplant, 2015
Hamdi H et al, Cardiovasc Res, 2013

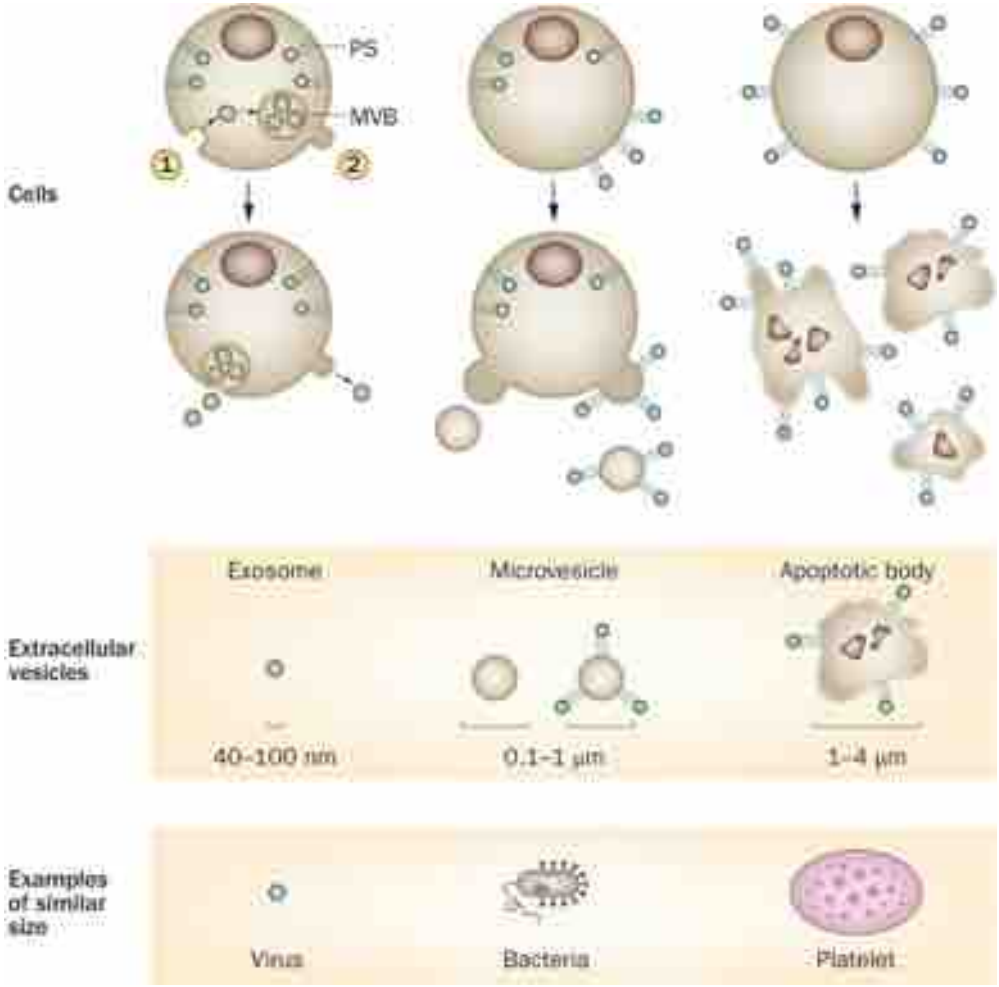
Menasché P et al, J Am Coll Cardiol, 2018

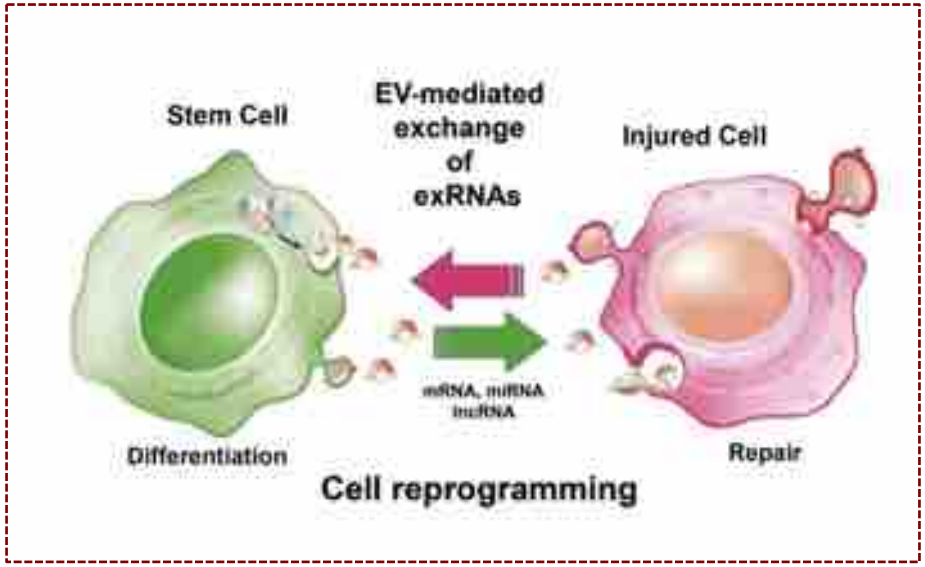
7- Vers une thérapie a-cellulaire?



Silvestre JS/Menasché P, Ebiomedicine, 2015

Cellules souches pluripotentes: Rôles des vésicules membranaires

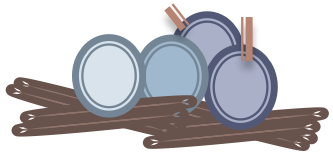


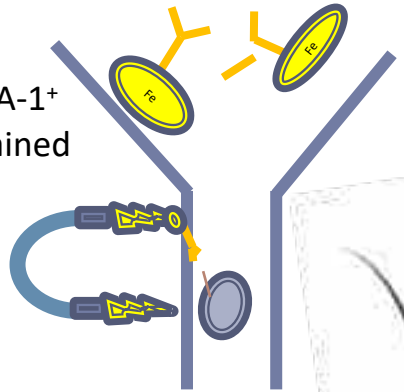


Production par les CS de vésicules membranaires (EV): Exosomes et Microparticules

Cellules souches pluripotentes: Rôles des vésicules membranaires

hESC-SSEA-1+



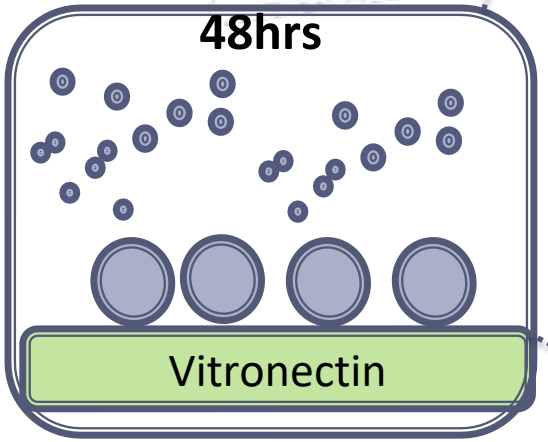


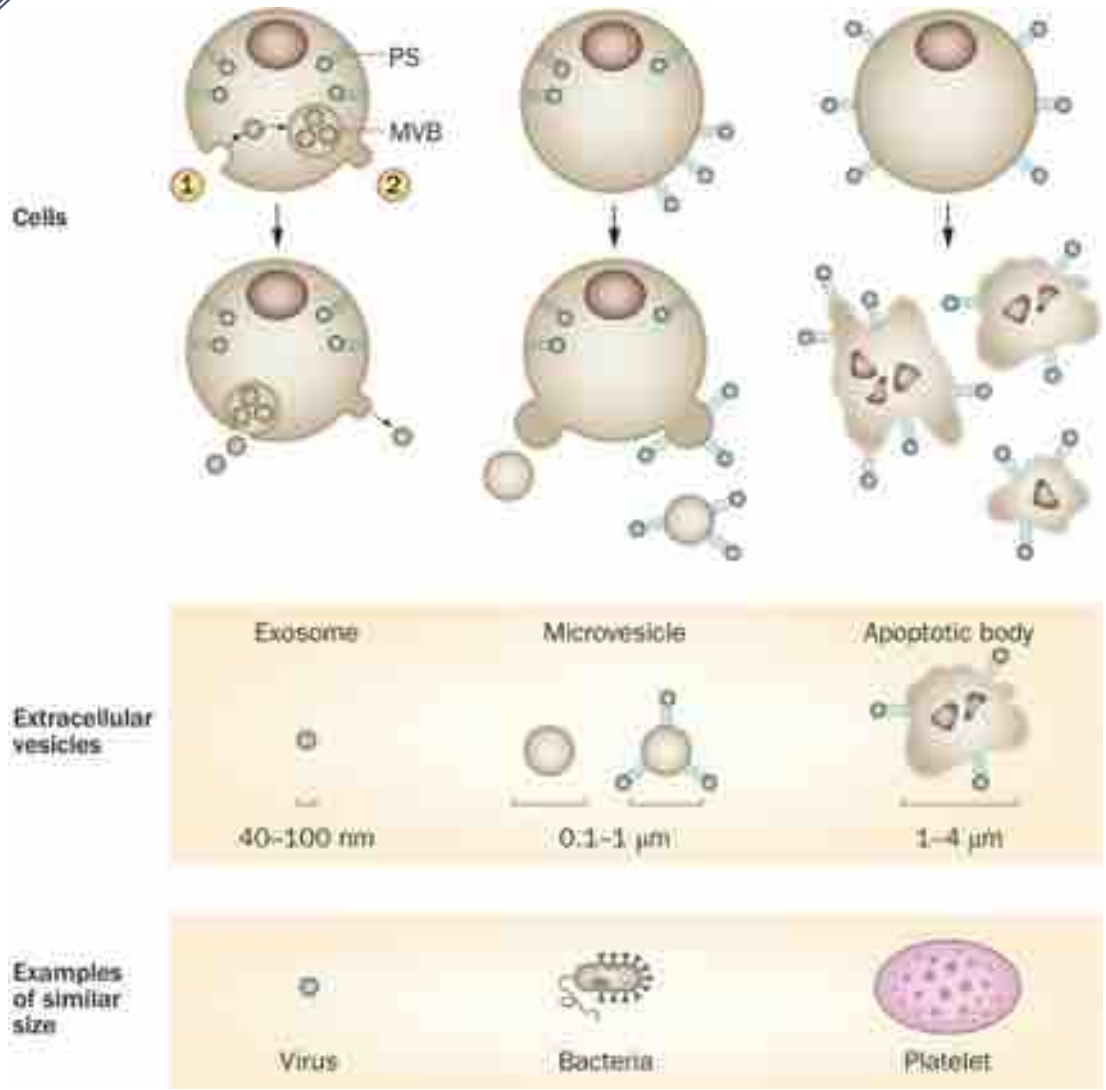
SSEA-1^{+} retained

5.10^{5} hESC-SSEA-1+

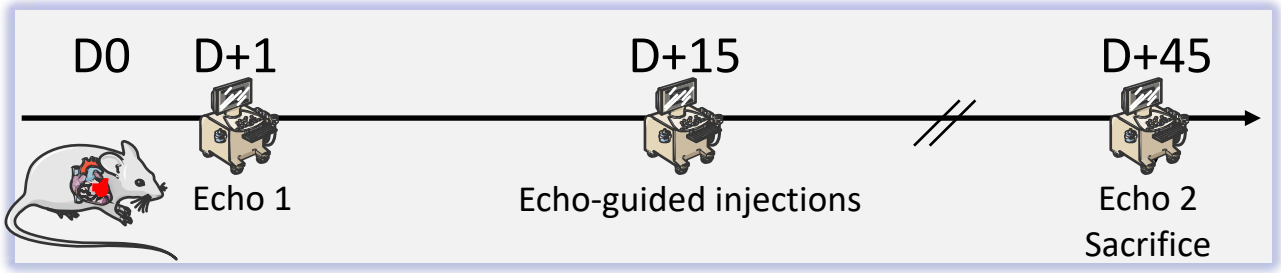
Around 10^{8} EVs

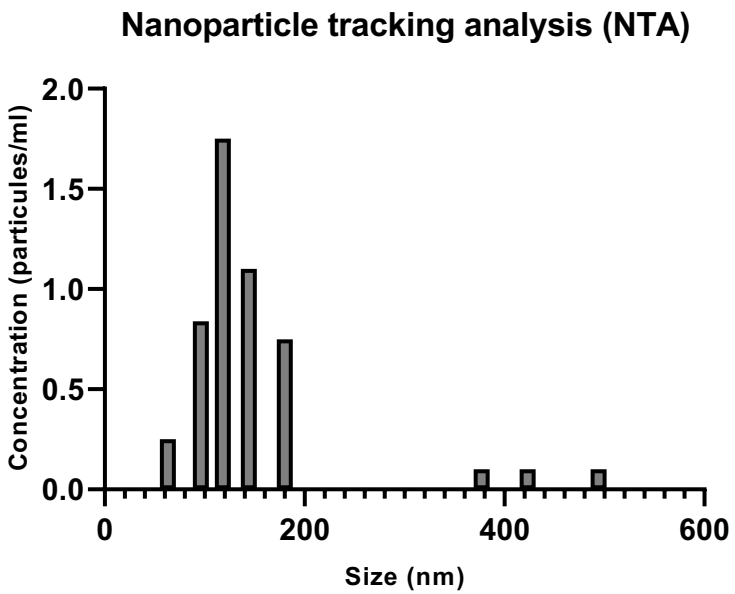
48hrs

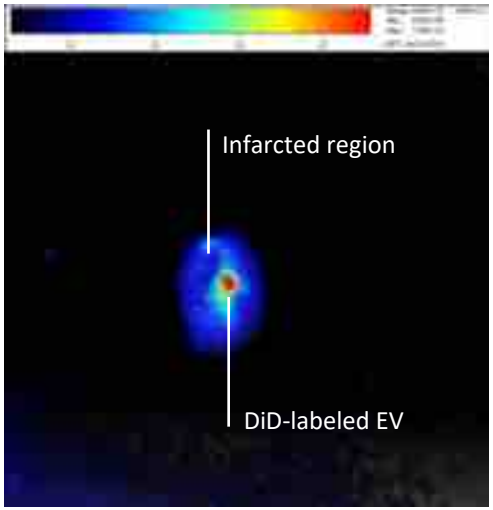


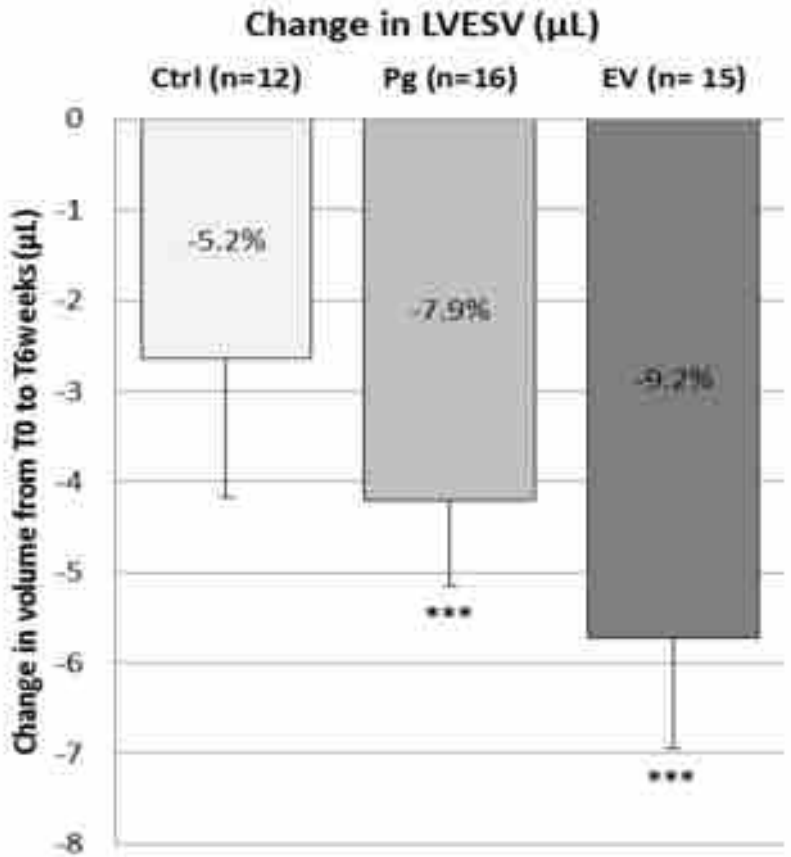


Cellules souches pluripotentes: Rôles des vésicules membranaires



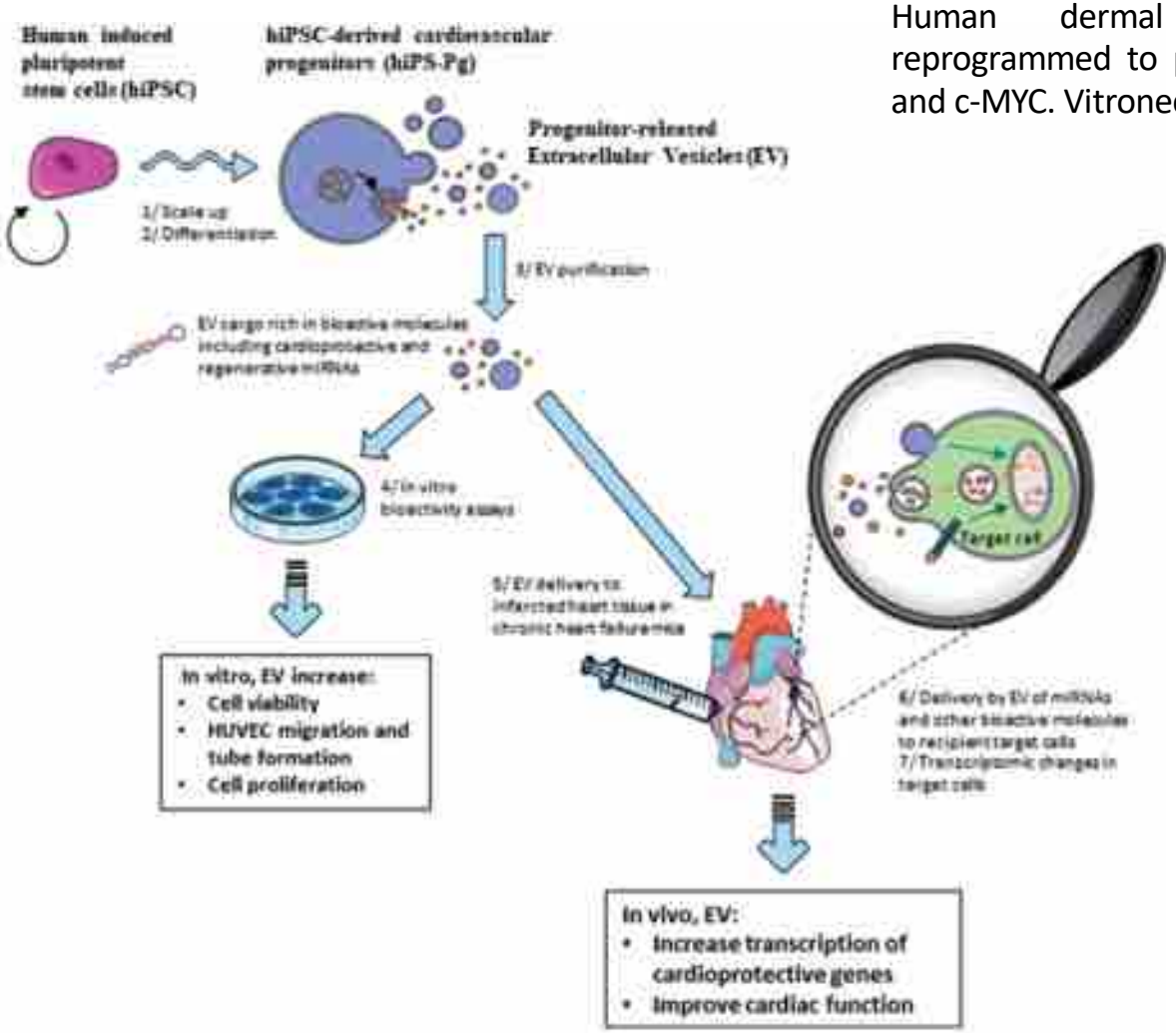






Kervadec A et al, J Heart Lung Transplant, 2016

Cellules souches pluripotentes: Rôles des vésicules membranaires



Human dermal fibroblasts were retrovirally reprogrammed to pluripotency with OCT4, SOX2, KLF4, and c-MYC. Vitronectin, 4 days.

MI

Baseline echo + Injections

3 weeks

√iPSC Cardiomyocytes

Pos for TBx20, TNNT2, MYH6&7

√iPSC Cardiac Progenitors

Neg for Nanog, SOX2, OCT3/4, Lin28
Pos for ISL1, MEF2C, GATA4, NKX2.5

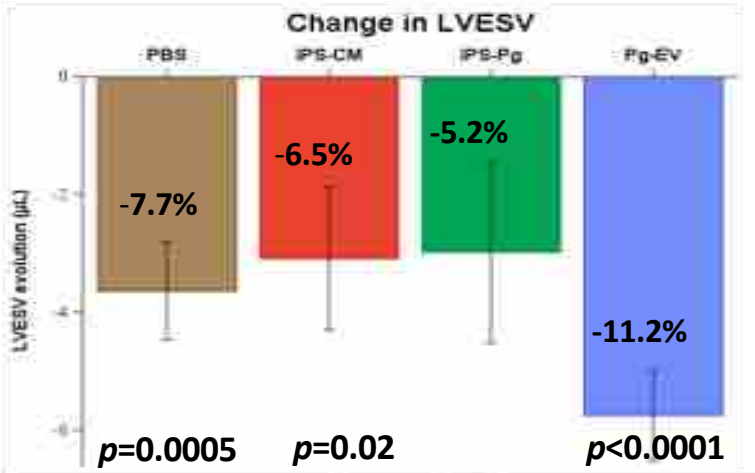
√Progenitor-Derived EVs

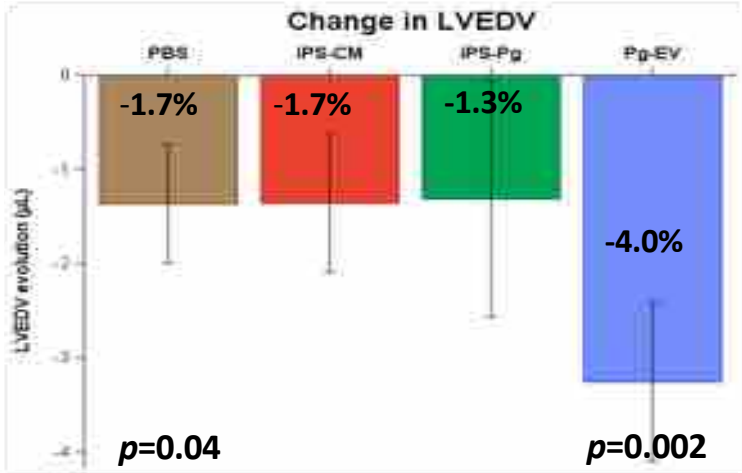
Echo 2 Sacrifice

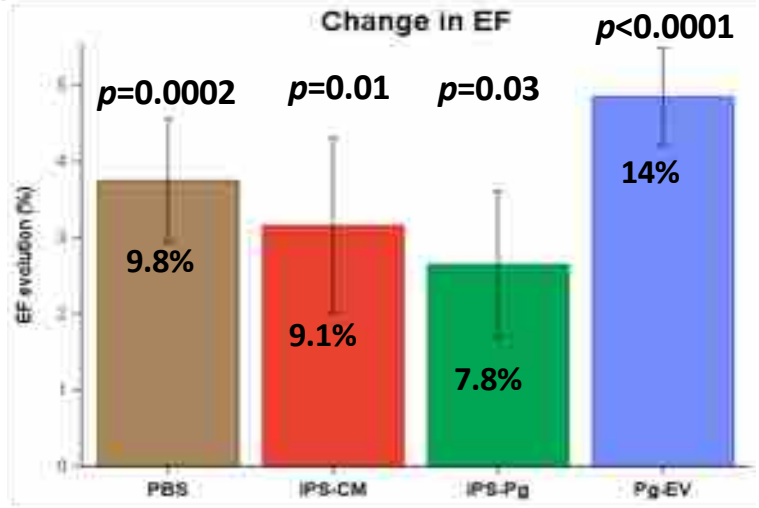
10 weeks

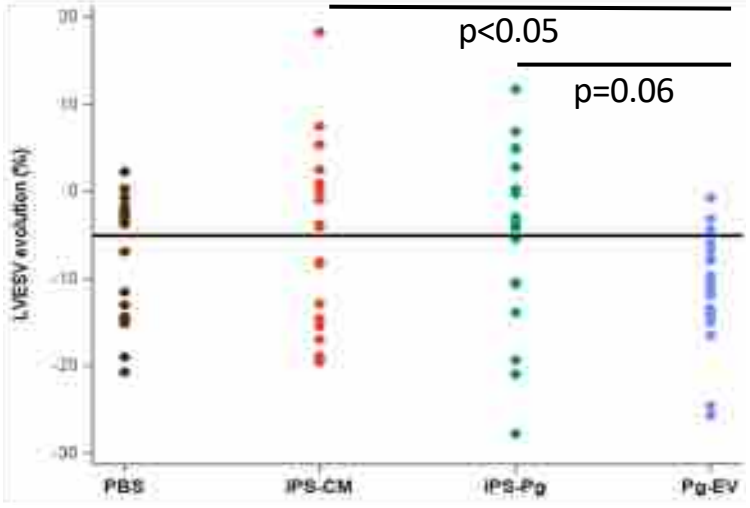
El Harane N et al, Eur Heart J, 2018

Cellules souches pluripotentes: Rôles des vésicules membranaires









PBS: n=17; iPS-CM: n=19; iPS-Pg: n=17; iPS-Pg-EV: n=19. All *p* values against corresponding baseline data

El Harane N et al, Eur Heart J, 2018

Thérapies cellulaires : retour vers le futur