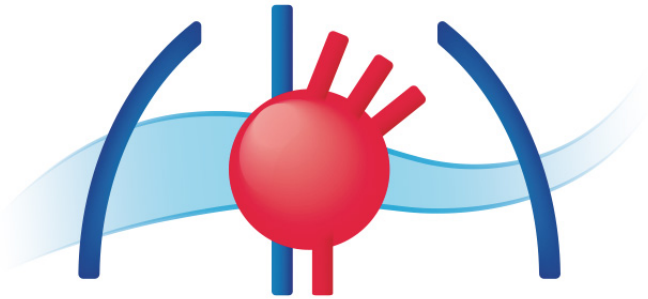
Thérapie cellulaire cardiaque après infarctus du myocarde

P. Lemarchand



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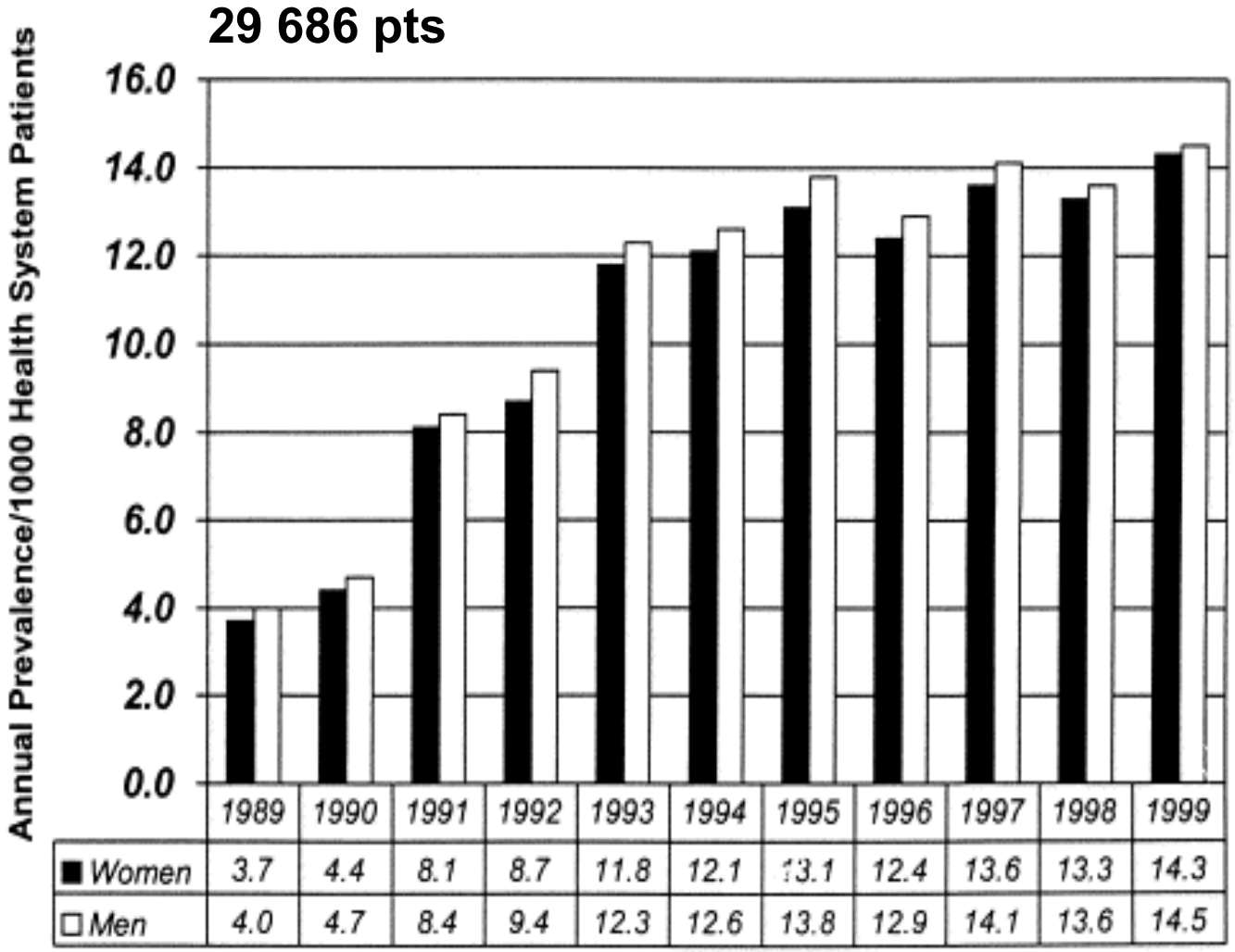
Prévalence de l'insuffisance cardiaque USA

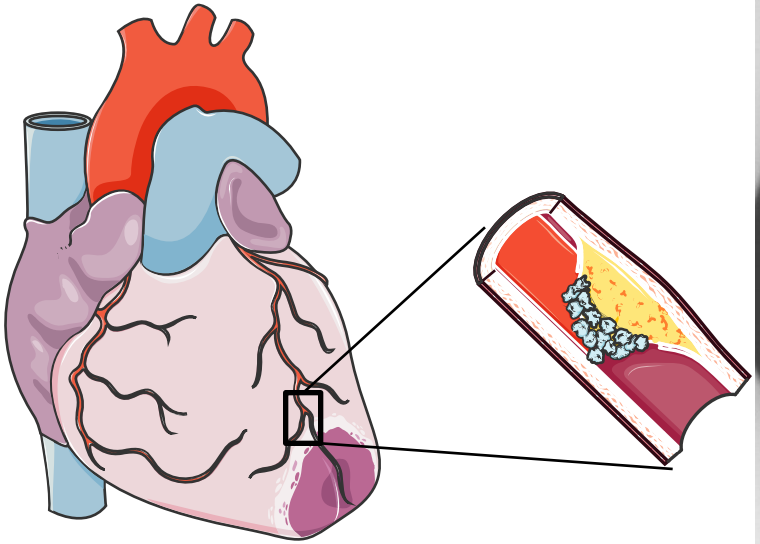


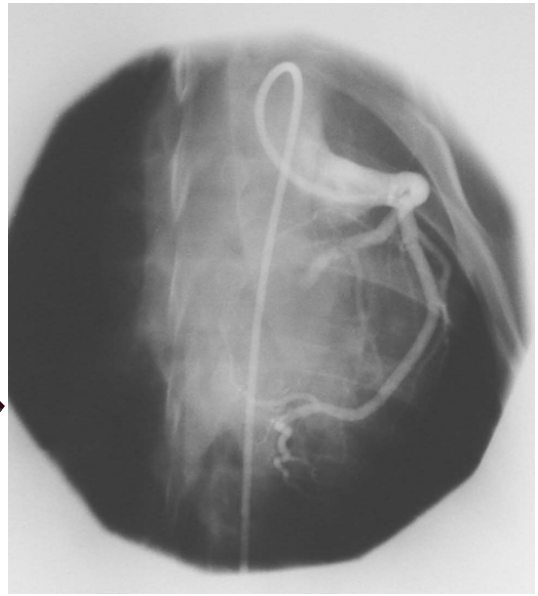
	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
■ Women	3.7	4.4	8.1	8.7	11.8	12.1	13.1	12.4	13.6	13.3	14.3
□ Men	4.0	4.7	8.4	9.4	12.3	12.6	13.8	12.9	14.1	13.6	14.5

McCullough et al. JACC 2002;39:60-9

Coronary Heart Disease

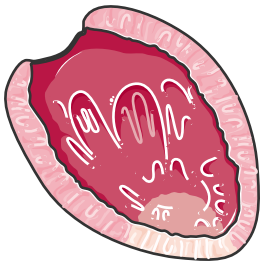
ACUTE MYOCARDIAL INFARCTION



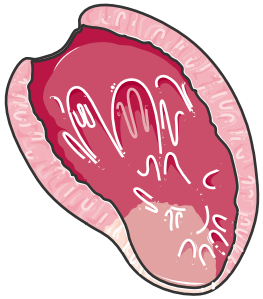


CARDIAC REMODELING

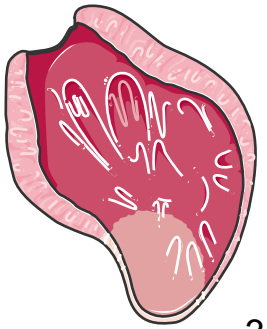
Hours



Days



Months



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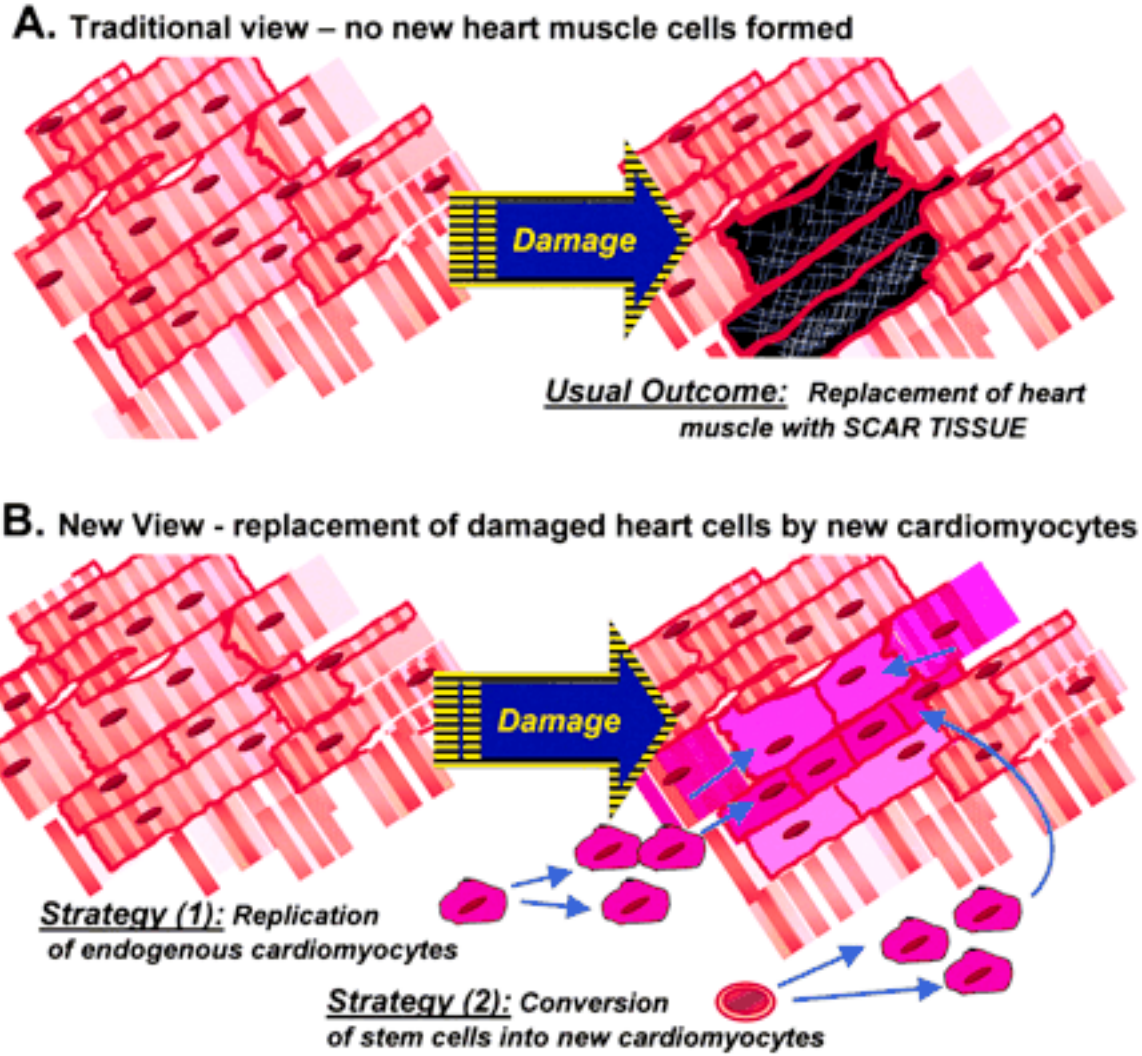
REPARATION CARDIAQUE



Grounds et al. J. Histo Cyto 2002:50:589

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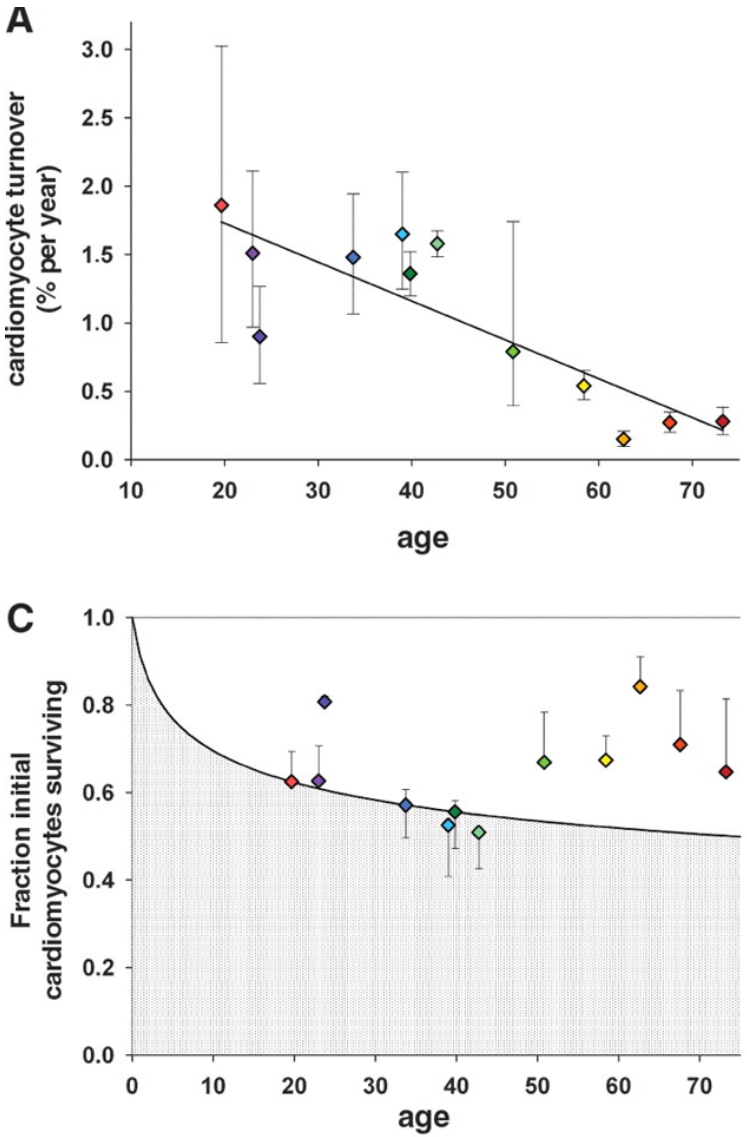
The heart is a regenerating organ

- Carbon 14 incorporation
- Cardiomyocyte renewal rate: 45%
- Turnover decreases after the age of 25

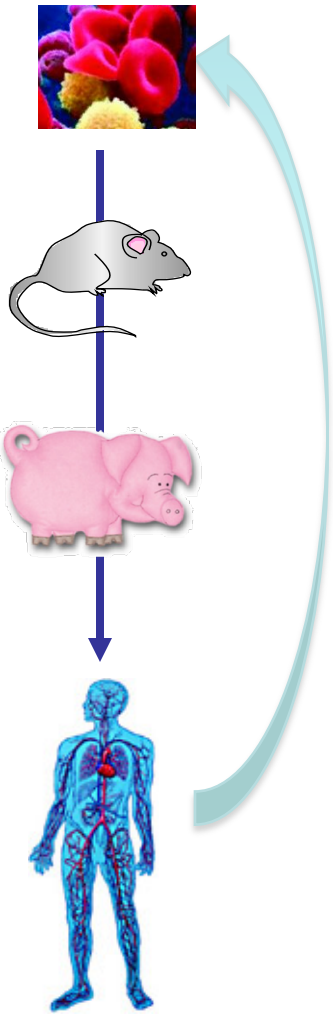
Spontaneous cardiac regeneration capabilities are restricted



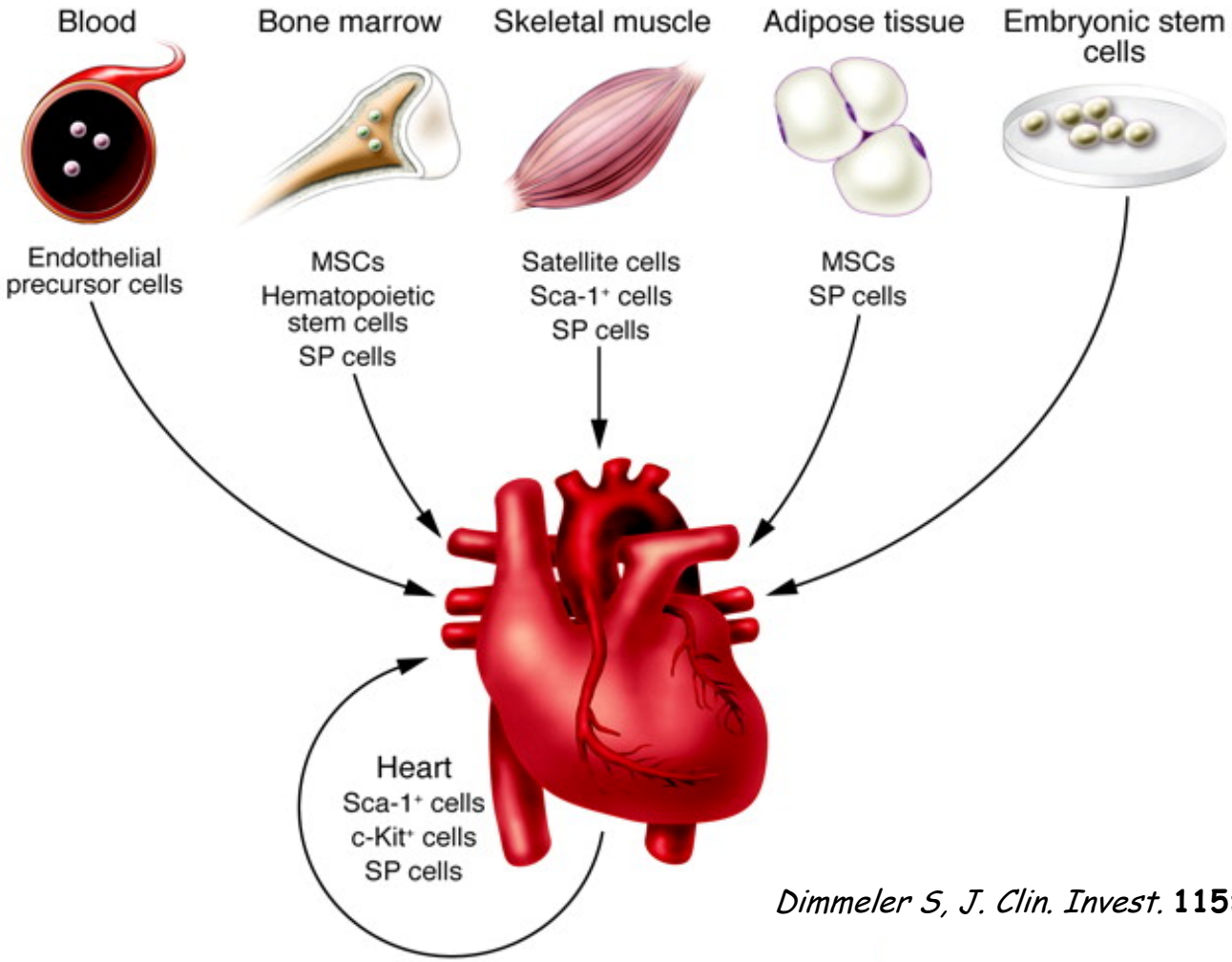
Science 2009;324:98-102

Stratégie de développement de la thérapie cellulaire cardiaque

- Cellules souches capables de réparer
- Essai chez le petit animal, après avoir induit un infarctus du myocarde
- Essai chez le gros animal
- Essai clinique chez un petit nombre de patients

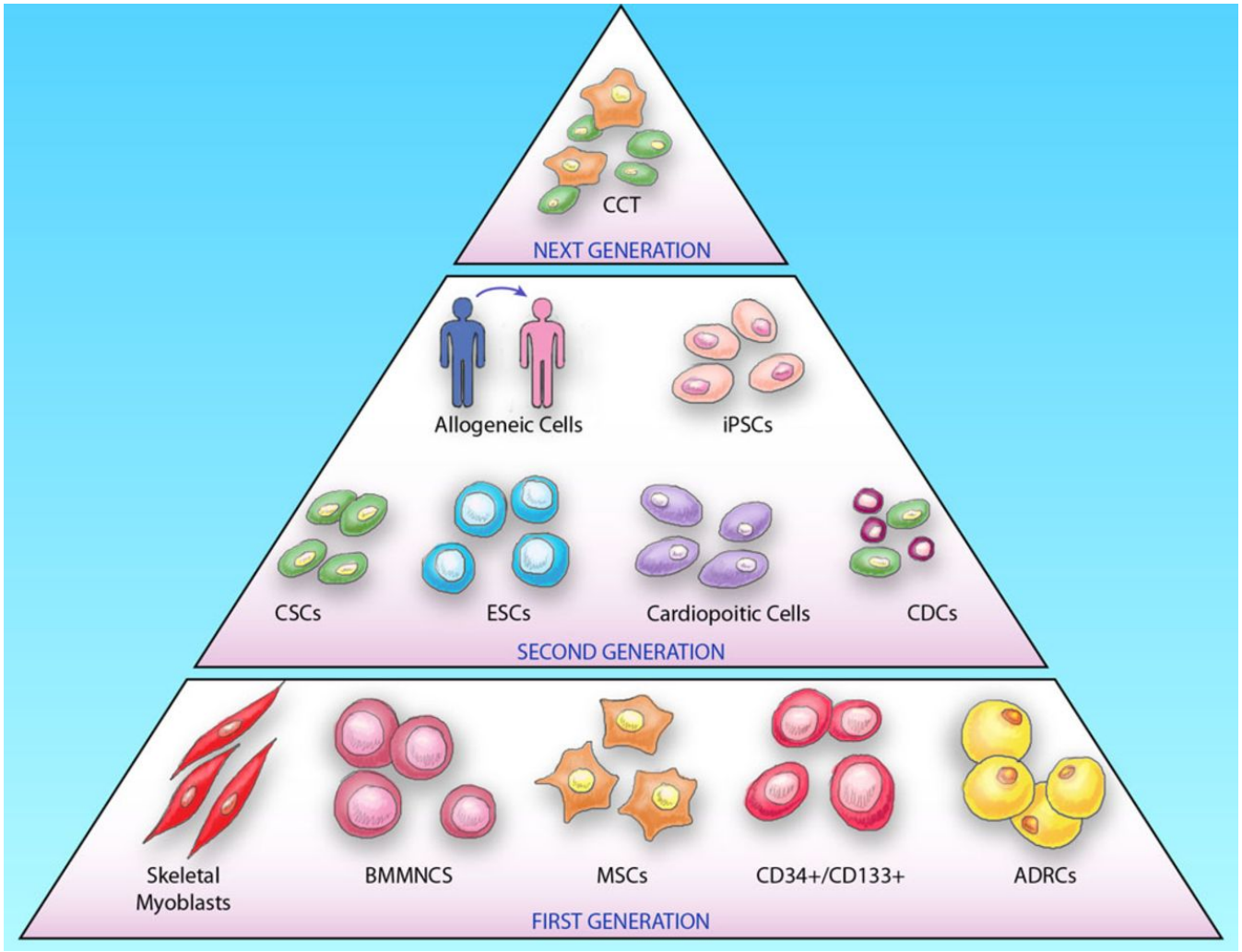


CELLULES UTILISABLES POUR LA THÉRAPIE CELLULAIRE CARDIAQUE



Dimmeler S, J. Clin. Invest. **115**:572-583 (2005)

CELLULES UTILISABLES POUR LA THÉRAPIE CELLULAIRE CARDIAQUE



Monisha N. Banerjee et al. Circ Res. 2018;123:266-287

American Heart Association.

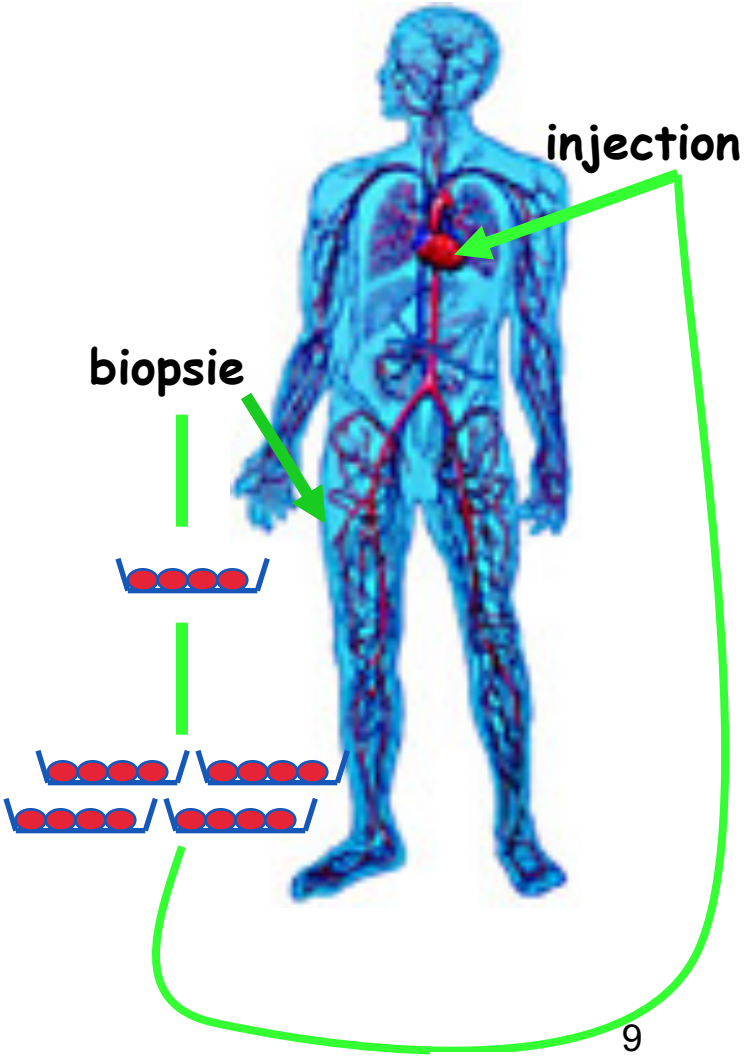
AUTOGREFFE DE MYOBLASTES

PRINCIPE

- Biopsie musculaire
- Culture *in vitro* et expansion des myoblastes
- Ré-injection en zone myocardique infarcie

AVANTAGES

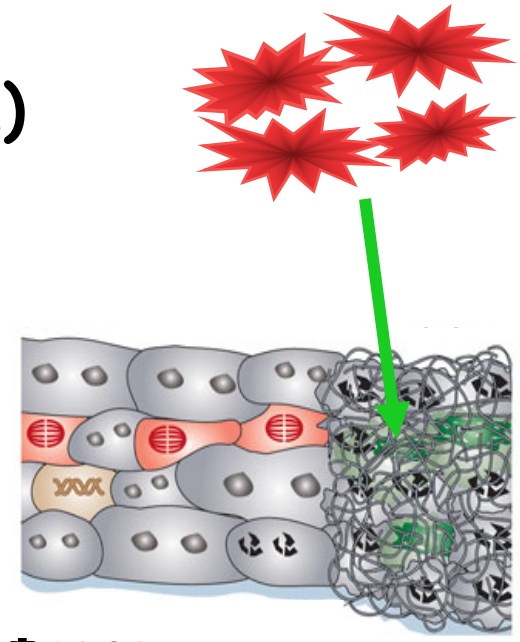
- Cellules musculaires satellites
- Autogreffe (immunité, éthique…)



AUTOGREFFE DE MYOBLASTES

RESULTATS EXPERIMENTAUX

- Faisable (rat, lapin, porc, mouton)
- Améliore la fonction myocardique



DIFFICULTES ACTUELLES

- Survie cellulaire faible
- Pas de différenciation cardiomyocytaire
- Mécanisme d'amélioration inconnu
- Troubles du rythme ventriculaire

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ESSAIS CLINIQUES PHASE I/II

Study	Year	LVEF	Nb of cells	Nb of Pt	Other surgery	TV	
Ménasché	2003	24±4%	$8.7 \pm 1.9 \times 10^8$	10	CABG	4 TV	
Smits	2003	36±11%	$2.0 \pm 1.1 \times 10^8$	13	/	4 TV (2 DC)	No
Pagani	2003		$< 3 \times 10^8$	5	LVAD		?
Herreros	2003	36±8%	$1.9 \pm 1.2 \times 10^8$	12	CABG		Amiodarone
Siminiak (POZNAN trial)	2004	25-40%	0.04 à 0.5×10^8	10	CABG	4 TV	Amiodarone for some Pt
Chachques	2004	28±3%	3×10^8	20	CABG		Amiodarone
Dibs	2005	28% ?	0.01 à 3×10^8 3×10^8	24 6	CABG LVAD	2 TV 1 TV	? ?
Ménasché (MAGIC trial)	*2008*	*15 à 35%*	*Control* *4×10^8* *8×10^8*	*97*	CABG	*6 TV*	*Amiodarone*

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La thérapie cellulaire cardiaque déclenche des arythmies ?

Effet indésirable mettant en jeu le pronostic vital

Quel(s) mécanisme(s) ?

Lésion tissulaire due à l' injection ?

Hétérogénéité électrophysiologique ?

Etude expérimentale évaluant le potentiel arythmogène de ces cellules

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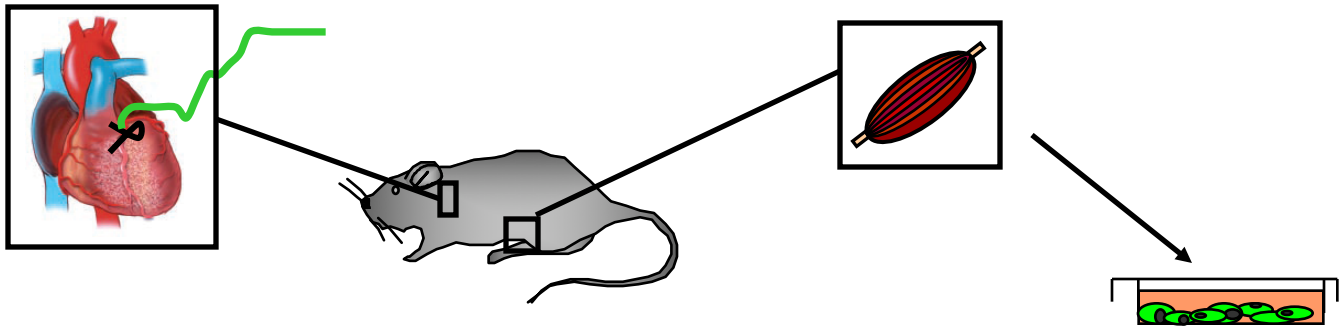
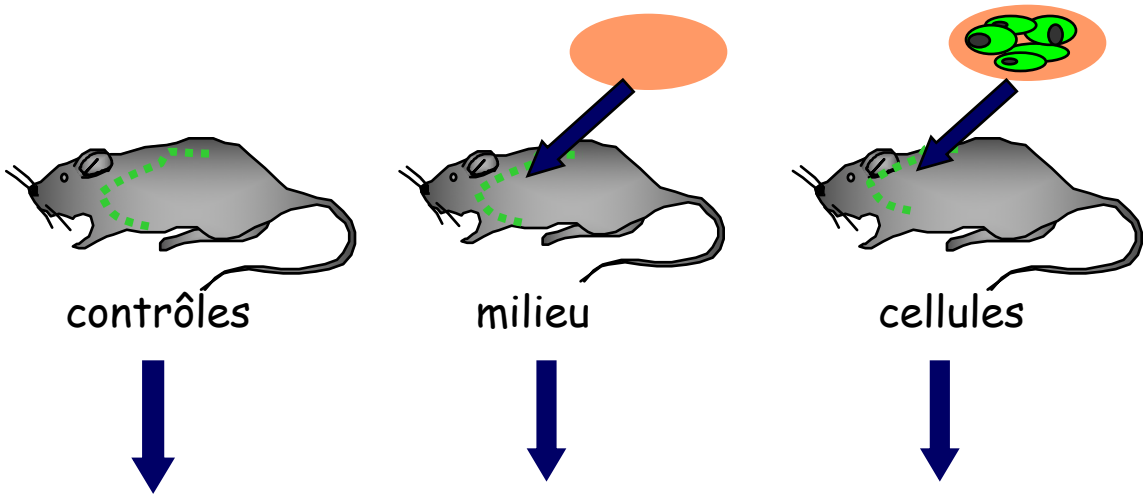
J 0



J 7



J 14
21
28
35

Stimulation Ventriculaire Programmée

Rythme spontané

Rythme imposé (100ms)

Enregistrement d' ECG de surface

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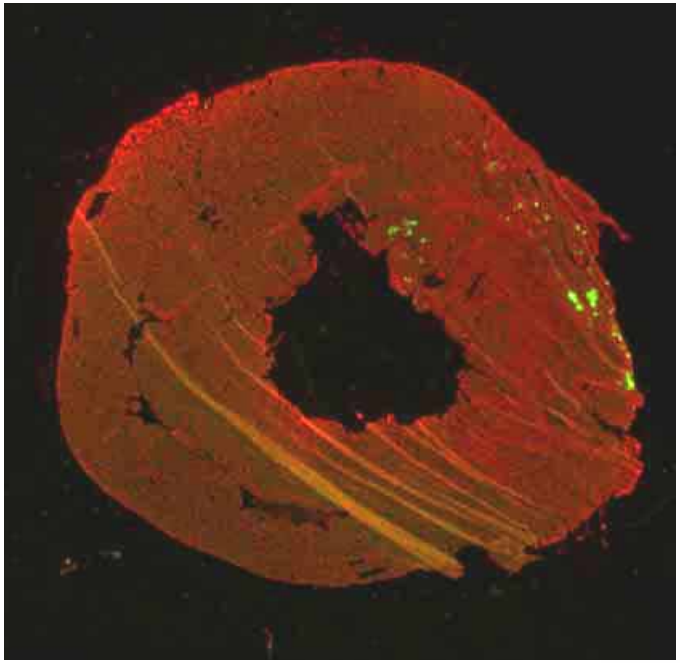
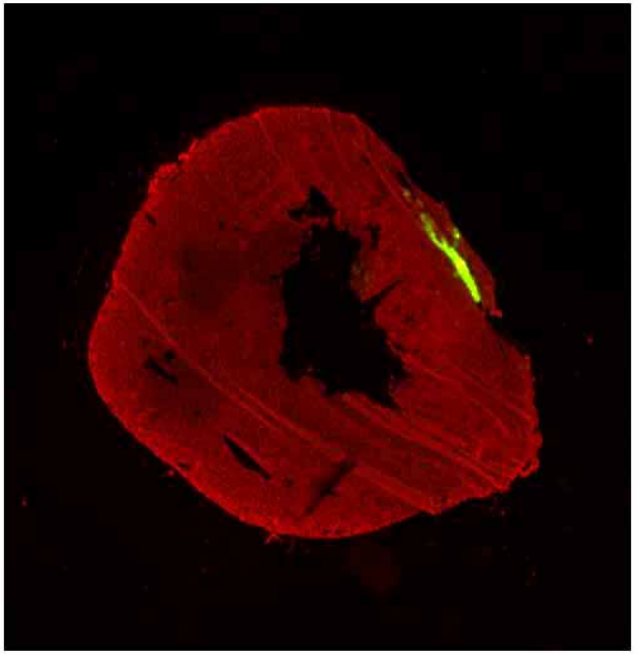
24h après injection

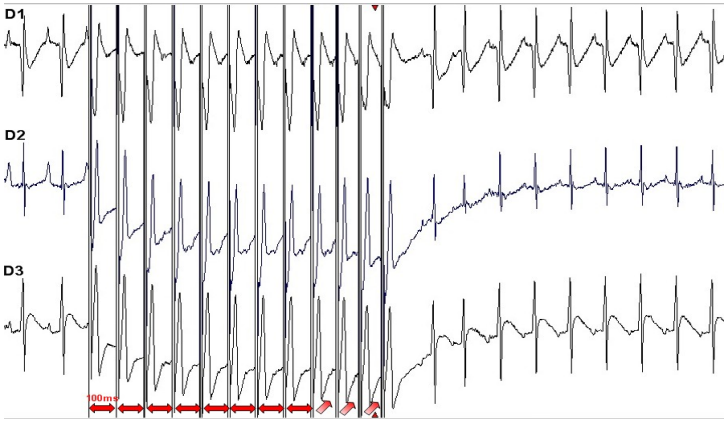




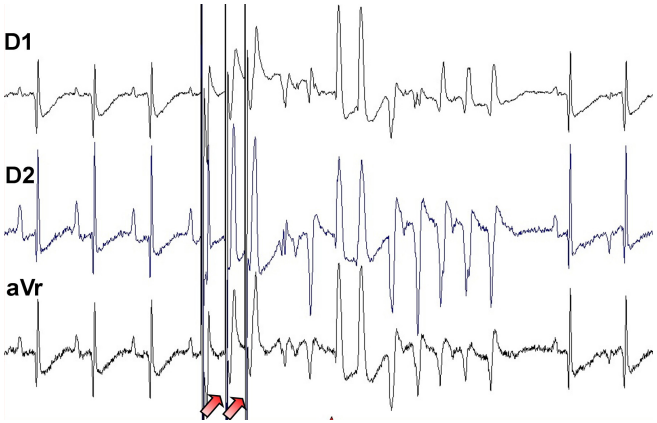
Myoblastes (vert)

Marqueur d' ADN (rouge)

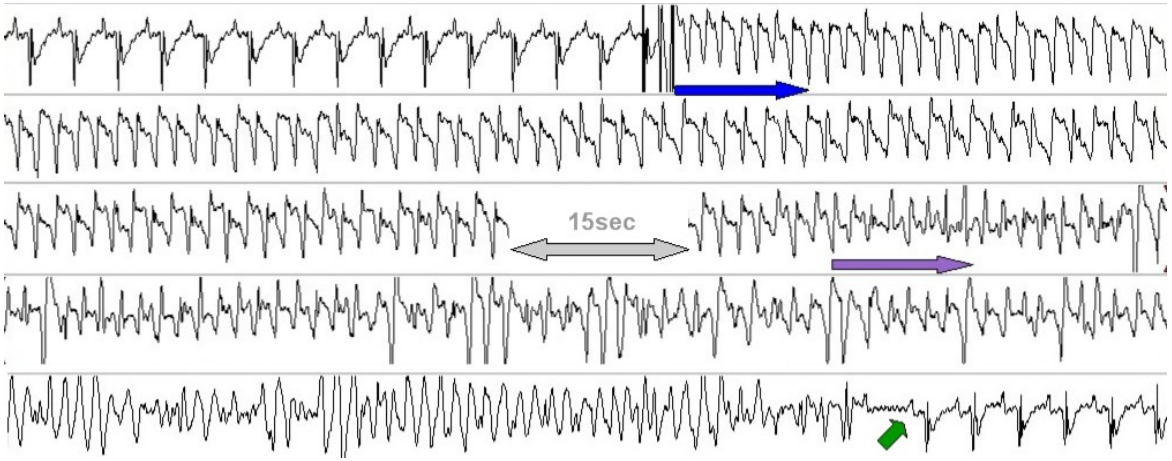
Stimulation Ventriculaire Programmée (1)



Pas de trouble du rythme déclenché



Tachycardie ventriculaire non soutenue



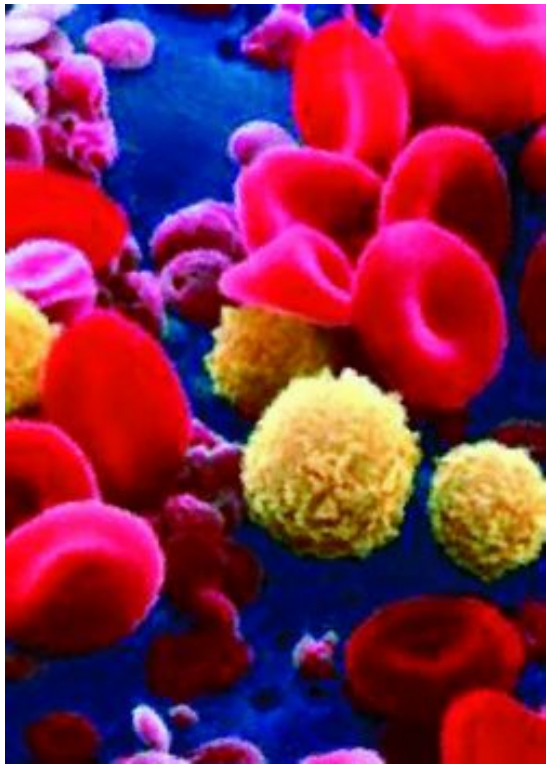
Tachycardie ventriculaire soutenue

Fibrillation ventriculaire

INTERET DE LA MOELLE OSSEUSE

La MO contient:

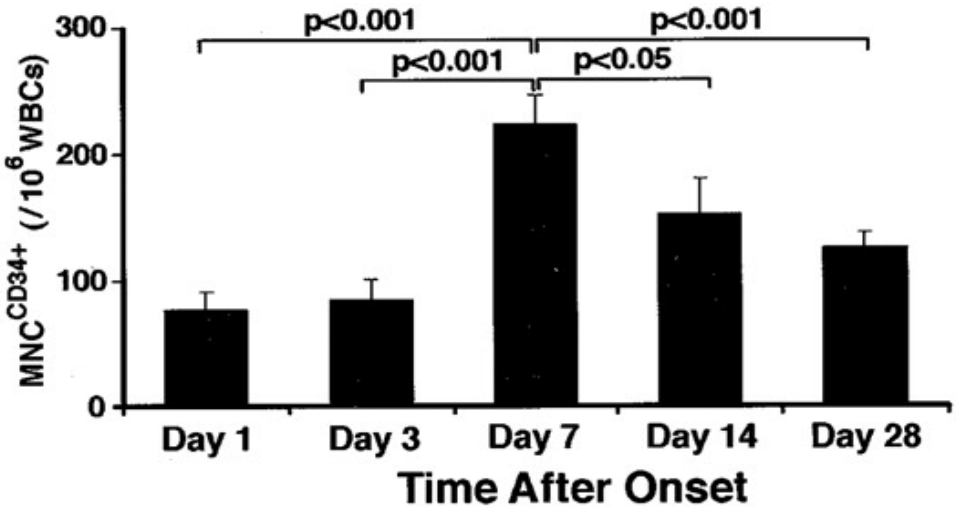
- cellules souches hématopoiétiques
- cellules souches mésenchymateuses
- progéniteurs endothéliaux

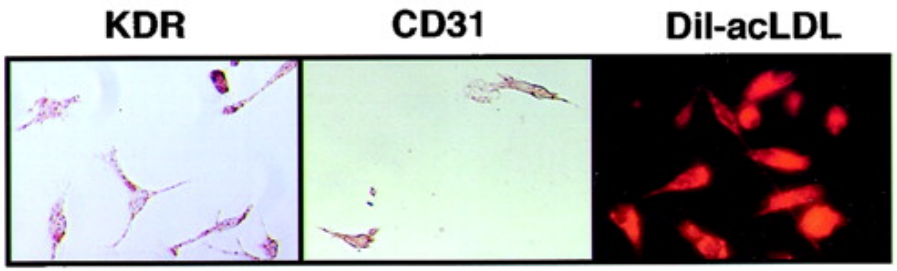


- Mobilisation des cellules souches

MOBILISATION SPONTANEE APRES IDM (1)

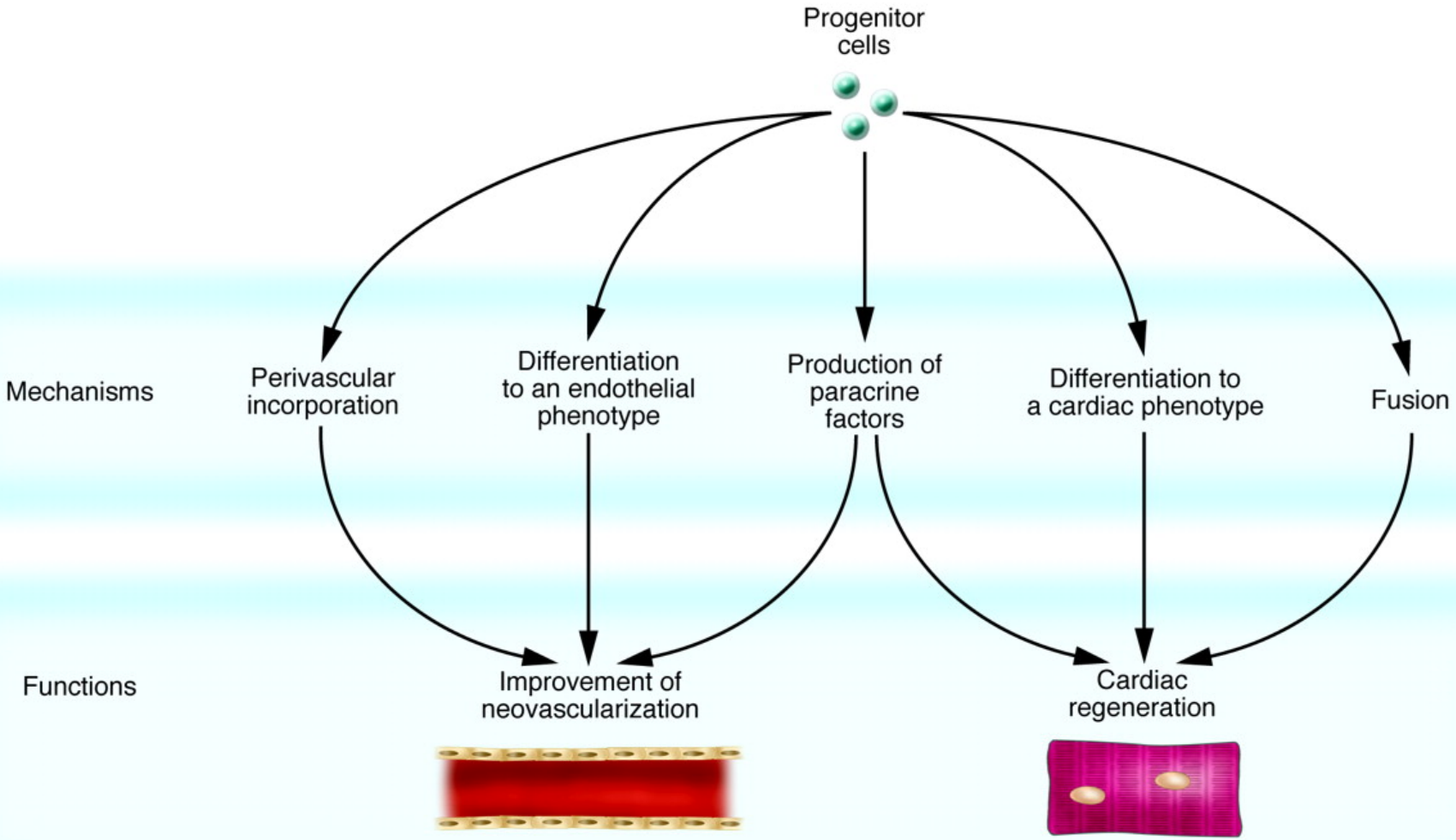
- 16 patients avec IDM
- Contrôles avec douleur atypique
- Prélèvement sang périphérique





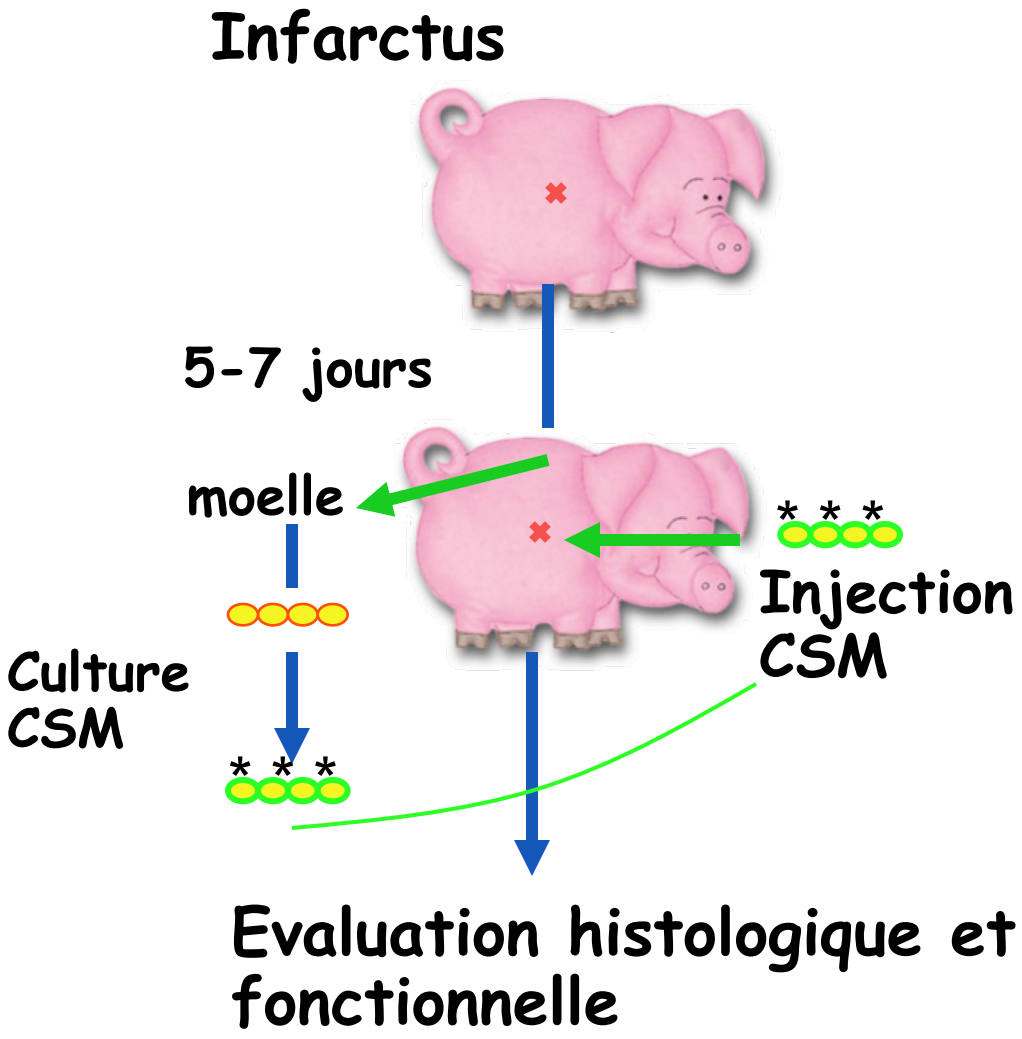
Circulation 2001; 103: 2776-2779

MÉCANISMES CELLULAIRES POTENTIELS



Dimmeler S, J. Clin. Invest. **115**:572-583 (2005)

ETUDE EXPERIMENTALE CHEZ LE GROS ANIMAL



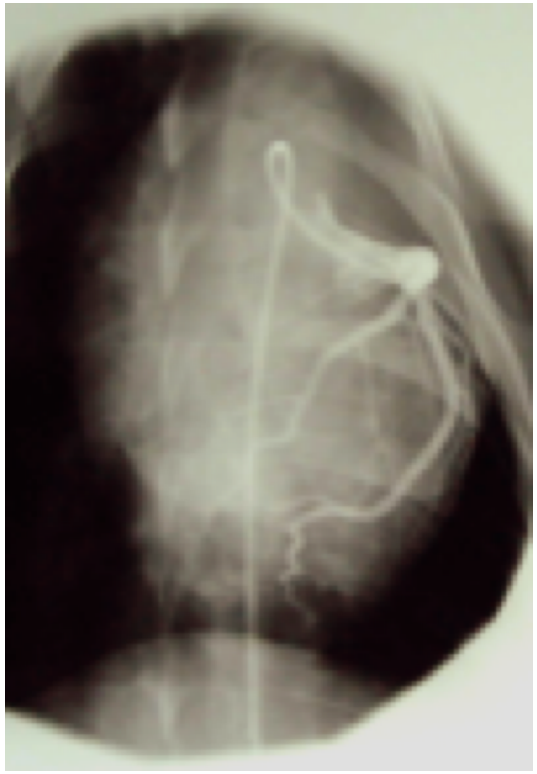
Entrainement à l'injection des CSM

Biodistribution

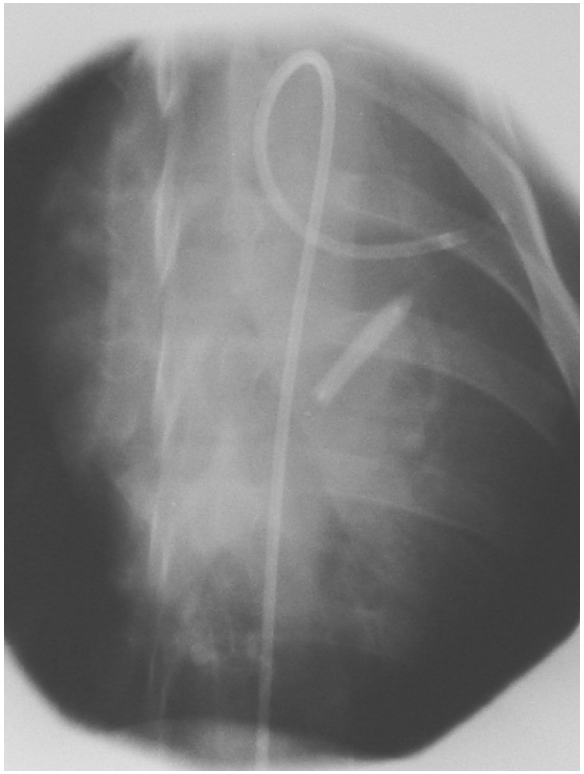
Survie des CSM

Forest *et al. Stem Cell Research & Therapy 2010*

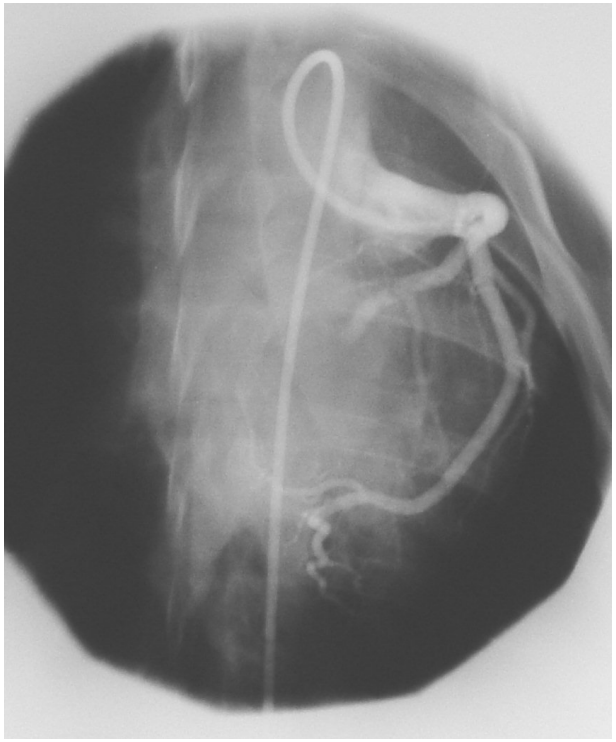
INDUCTION DE L'INFARCTUS



Avant thrombus



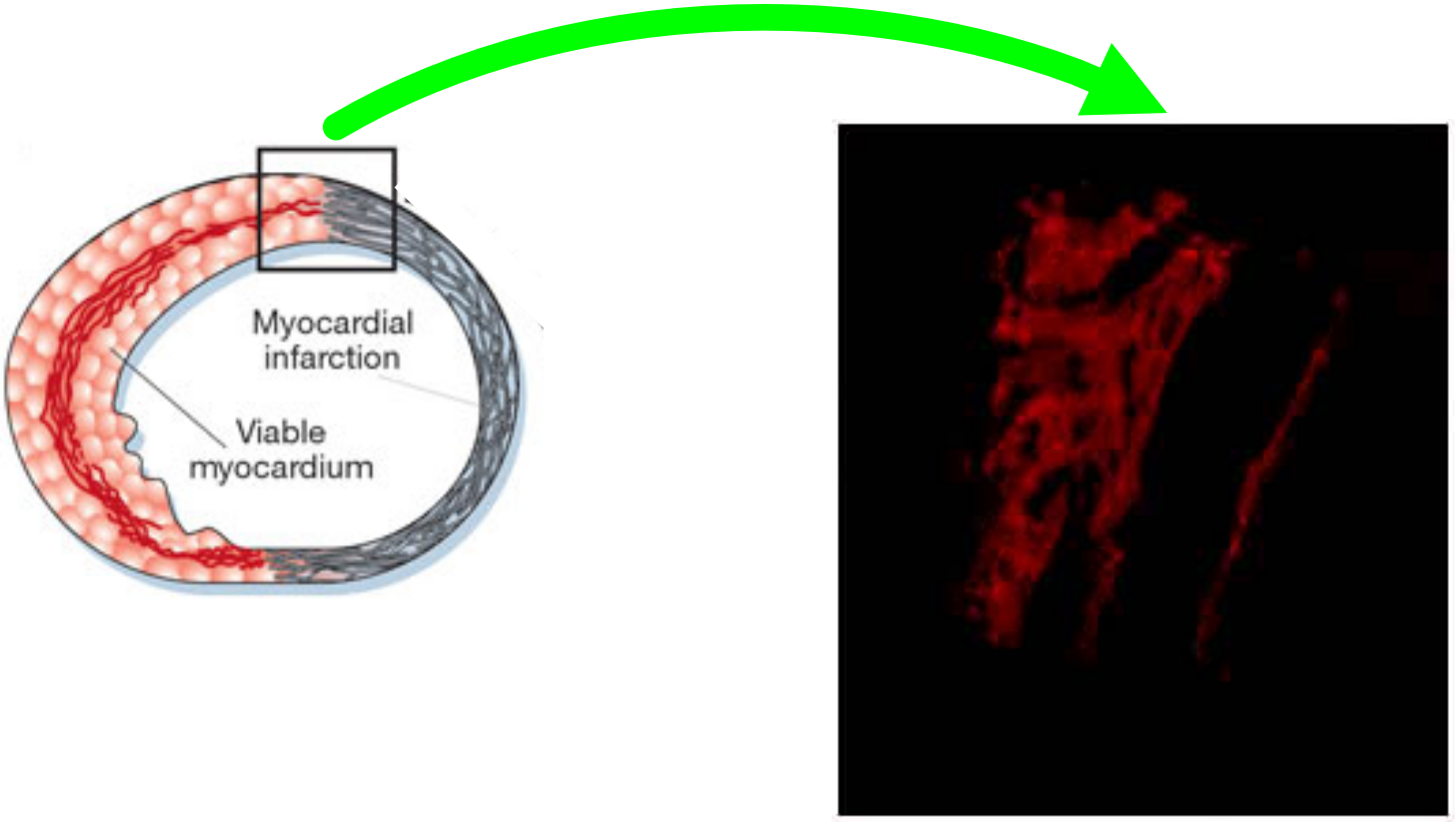
ballon



Après thrombus

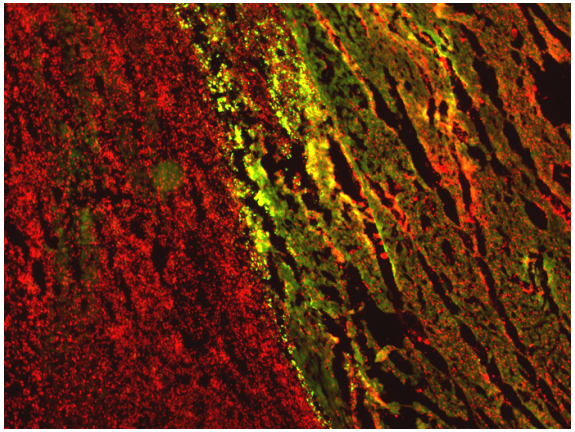
Forest *et al. Stem Cell Research & Therapy 2010*

INFARCTUS DU MYOCARDE

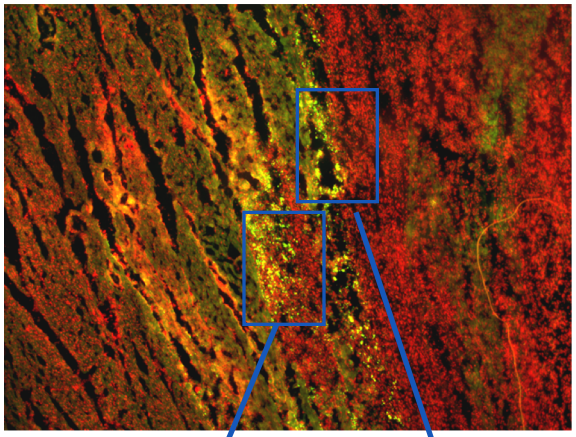


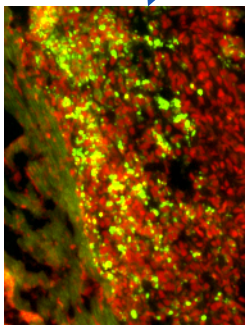
Marquage des noyaux

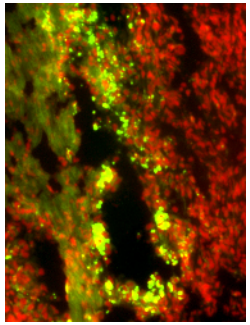
Présence des cellules dans la zone infarcie

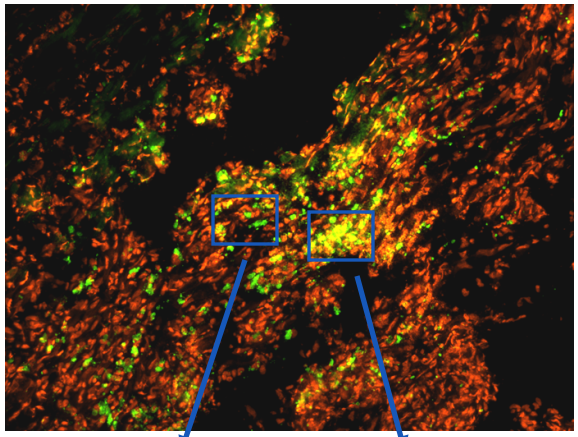


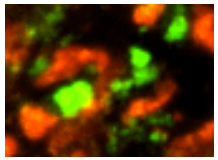
Noyaux (rouge) + cellules injectées (vert)



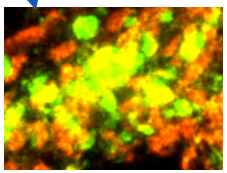






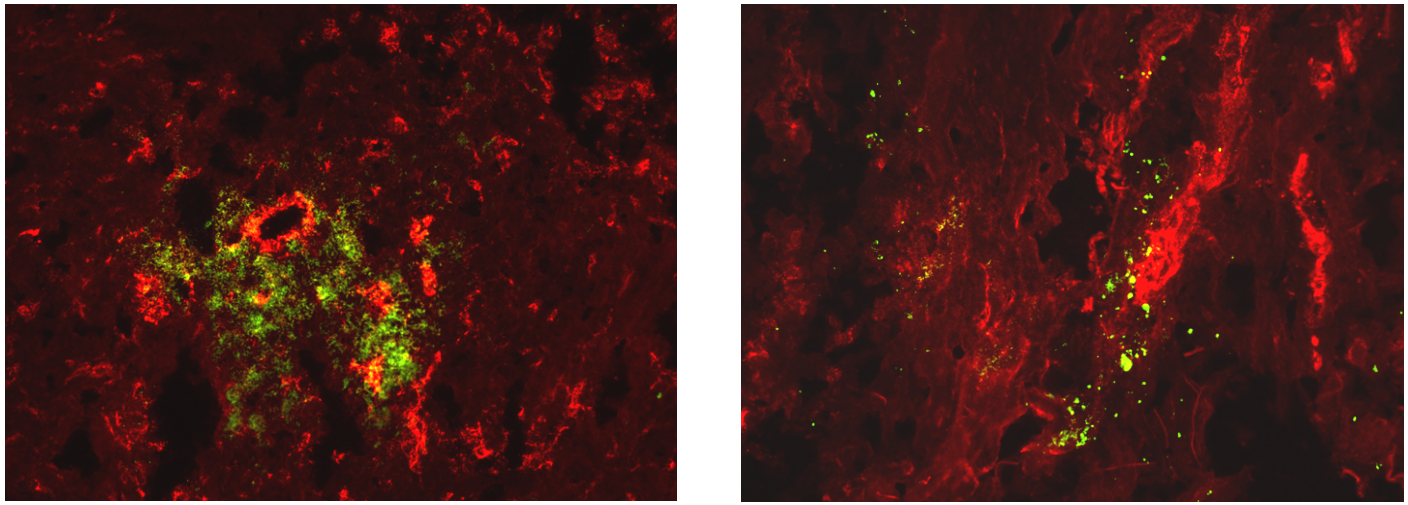


Débris cellulaires



Amas cellulaires

Les cellules sont dans le parenchyme

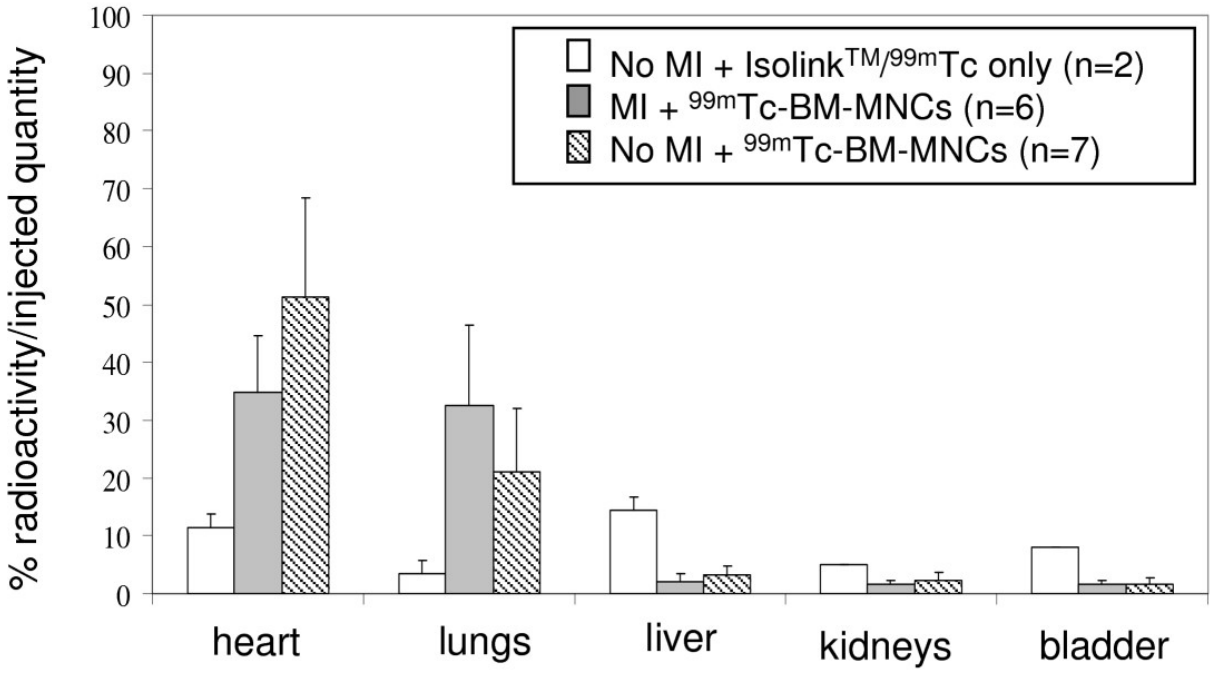


Cellules endothéliales (rouge, Willebrand) + cellules injectées (vert)

Biodistribution

Same pig model
Injection of stem cells, labelled with radio-element (99mTc)

1 hour after cell IC injection

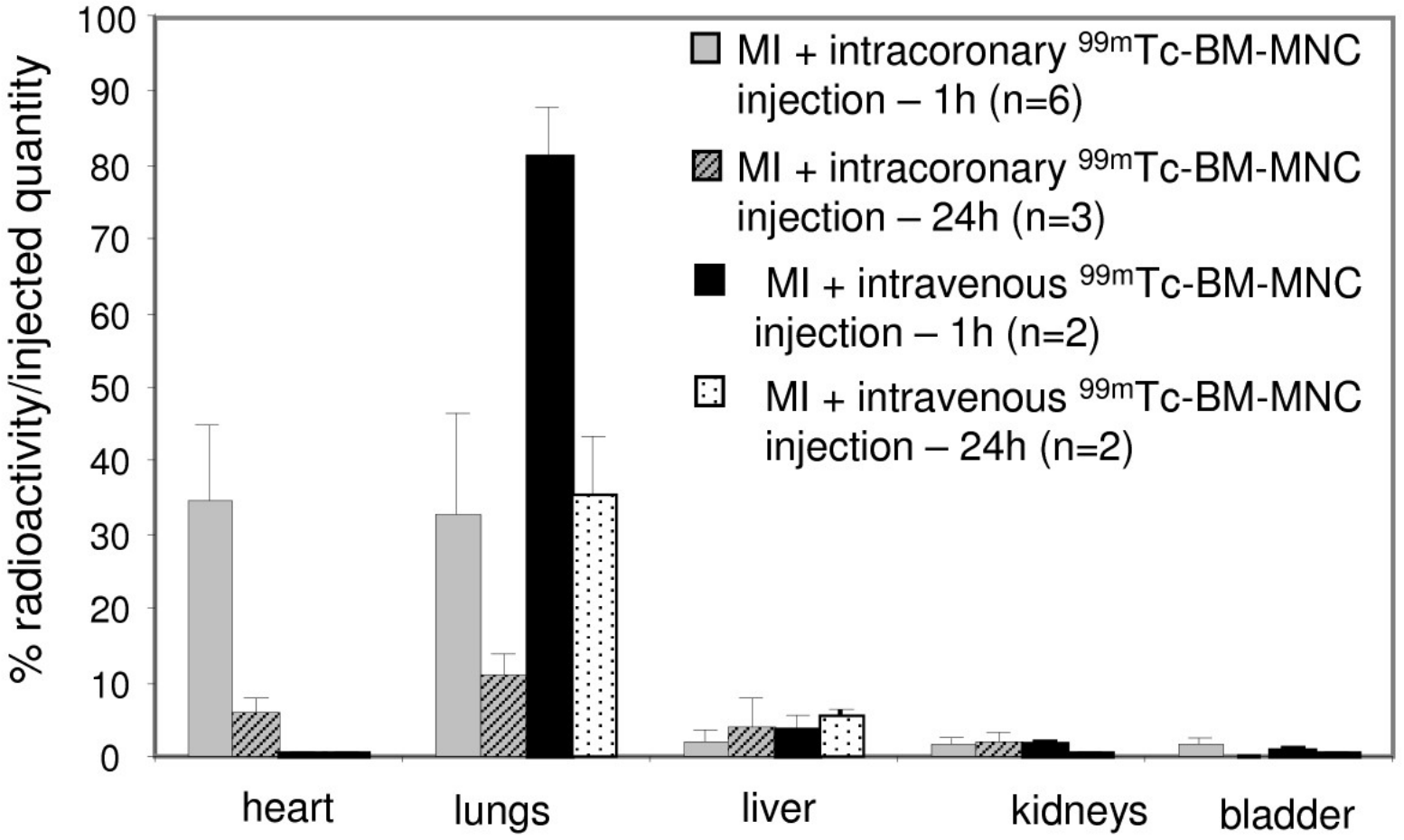


MI: myocardial infarction
BM-MNC: injected stem cells

Identical cell retention

Forest *et al. Stem Cell Research & Therapy 2010*

Intra-Coronary route outperforms IV route



MI: myocardial infarction
BM-MNC: injected stem cells

Forest *et al. Stem Cell Research & Therapy 2010*

Intra-Coronary vs. IV route

Intravenous BMC infusion is ineffective to target myocardium

→ Favor in situ delivery (IC or direct myocardial delivery)

Forest *et al. Stem Cell Research & Therapy 2010*

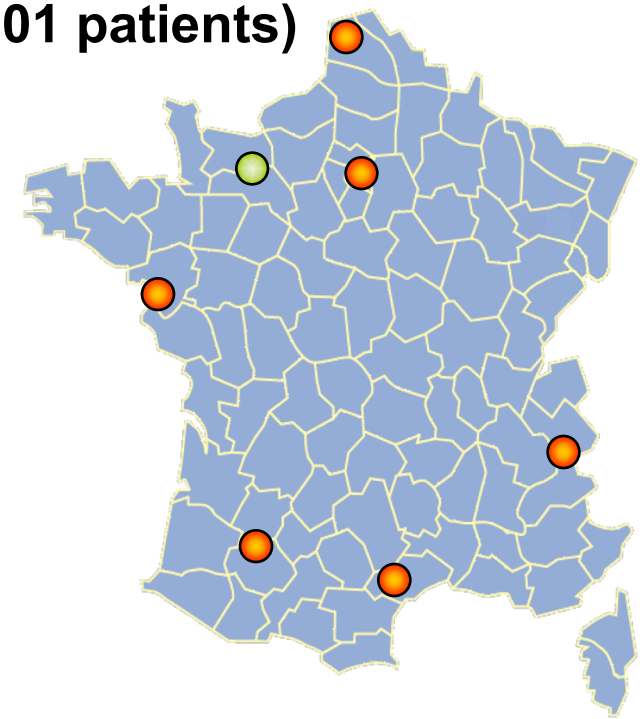
AIM OF THE BONAMI TRIAL

To assess the beneficial effect of cell therapy in patients with decreased left ventricular ejection fraction after acute myocardial infarction, and to identify predictive factors of successful therapy.

Roncalli et al. Eur Heart J 2011

STUDY DESIGN of the BONAMI TRIAL

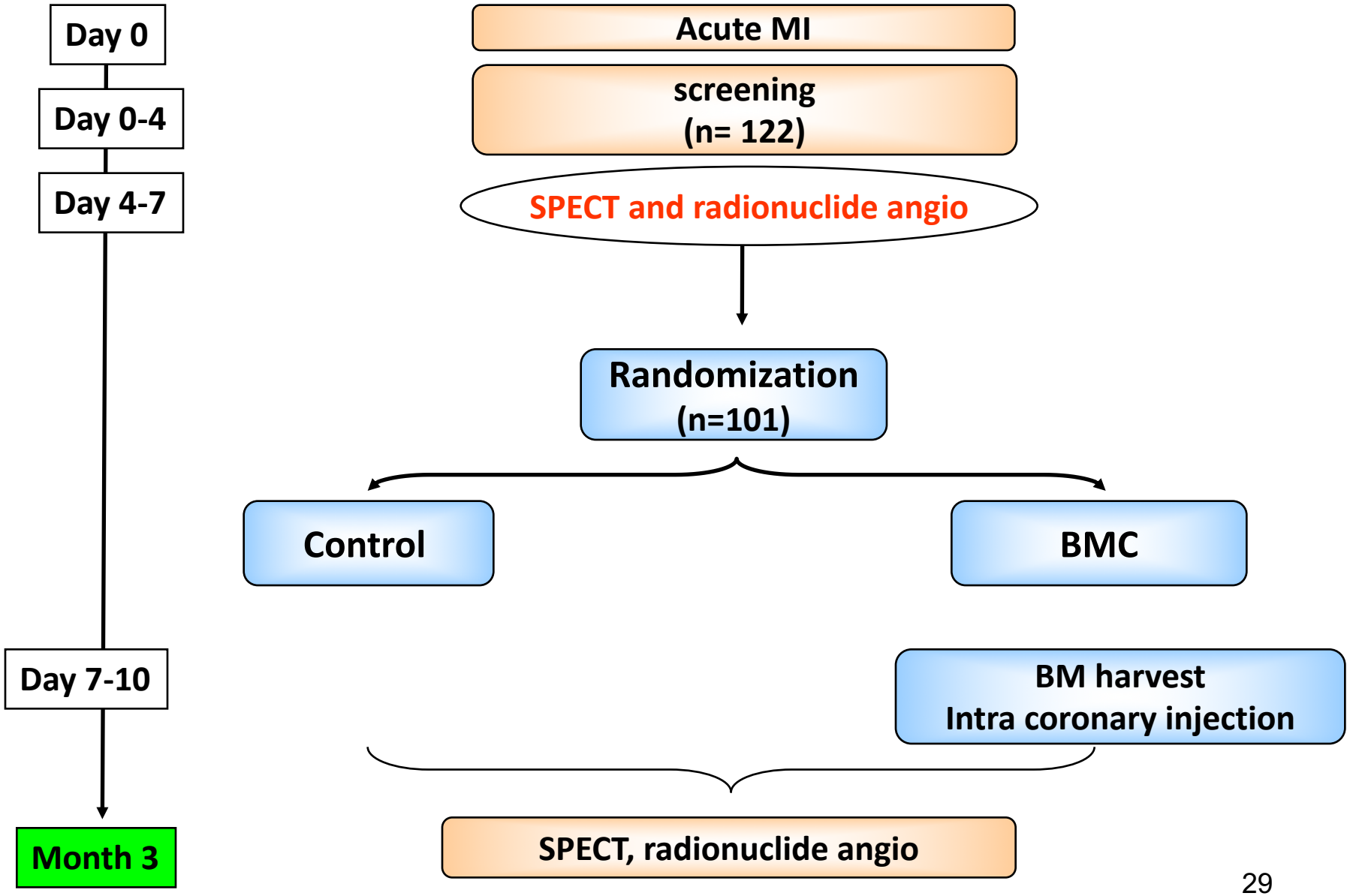
Randomized, multicenter controlled trial (101 patients)
6 academic hospitals in France



Main inclusion criteria:

- **Inaugural acute MI**
- **Single coronary lesion and successful angioplasty**
- **LVEF ≤ 45%**
- **Impairment of myocardial viability on SPECT**

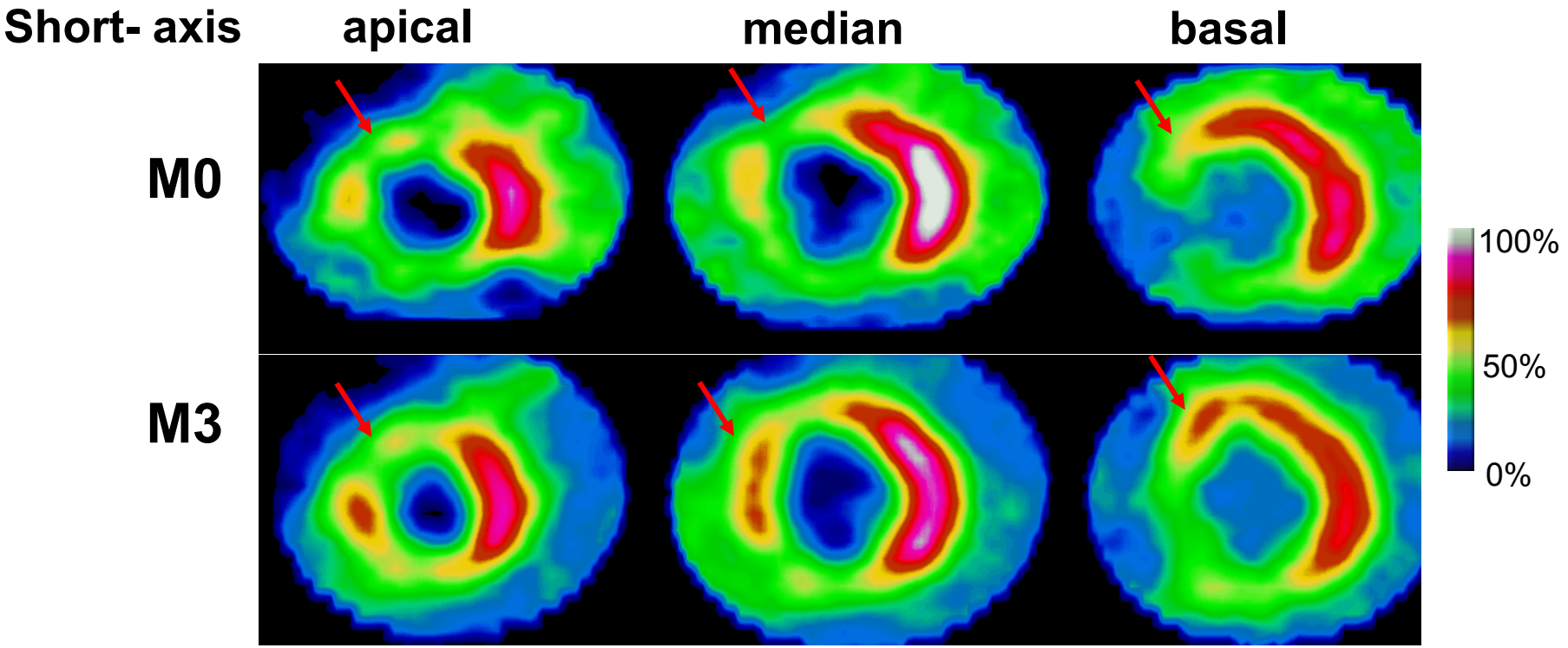
DESIGN OF THE BONAMI TRIAL



PRIMARY ENDPOINT

- **Myocardial viability** at 3 months after MI evaluated by resting **Thallium 201-SPECT**

- Criterion for cell therapy success:
viability improvement of **≥ 2/17 segments** (2 non viable become viable)



- All measurements were performed by **2 blinded investigators** of an **independent core lab**.

CELL THERAPY PROCEDURE

Cell therapy product:

- 50 cc of bone marrow were harvested (iliac crest punction) under local anesthesia
- Bone marrow mononucleated cells were isolated by ficoll gradient
- 100 x 10^6 autologous mononucleated cells (in 10cc)

- Intra coronary cell injection:

- The same day as BM collection
- Mean delay btw acute MI and BMC infusion: 9.3 ± 1.7 days

8H00 Bloc de chirurgie
vasculaire et digestive
CHU de Nantes
Prélevement des cellules
sur le patient

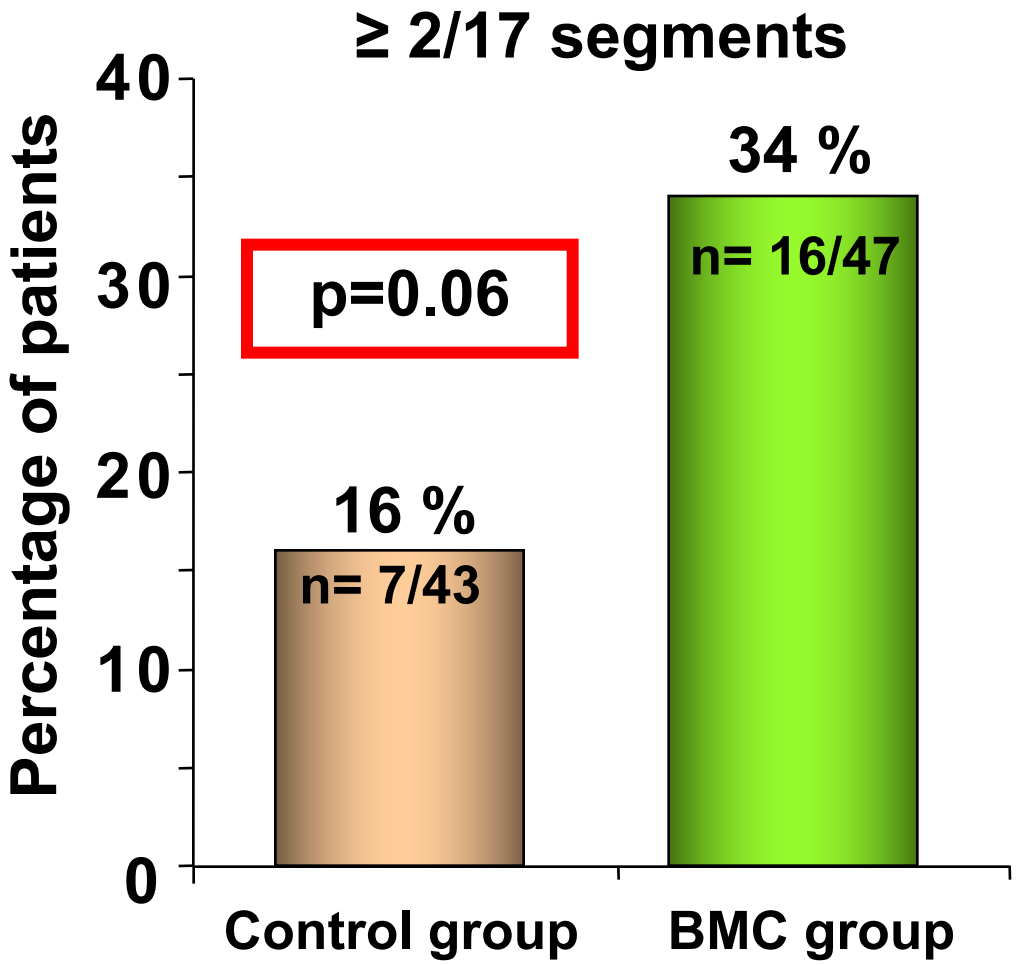
RESULTS: Baseline Characteristics

	Control (n= 49)	BMC (n= 52)	p
Age (years)	55 ±11	56 ±12	NS
Male gender, %	89.8	80.8	NS
Hypertension, % (n)	34.7 (17/49)	34.6 (18/52)	NS
Dyslipemia, % (n)	34.7 (17/49)	46.2 (24/52)	NS
Diabetes mellitus, % (n)	18.4 (9/49)	21.2 (11/52)	NS
Active smokers, % (n)	53.1 (26/49)	53.8 (28/52)	NS
Timing of revasc <12h ,% (n)	76 (37/49)	75 (39/52)	NS
Culprit artery (LAD) , % (n)	96 (45/47)	92 (45/49)	NS
LVEF (%, by RNA)	**37.0 ±6.7 (47)**	**35.6 ±7 (50)**	**NS**

RESULTS: Assessement of Cell Therapy Success

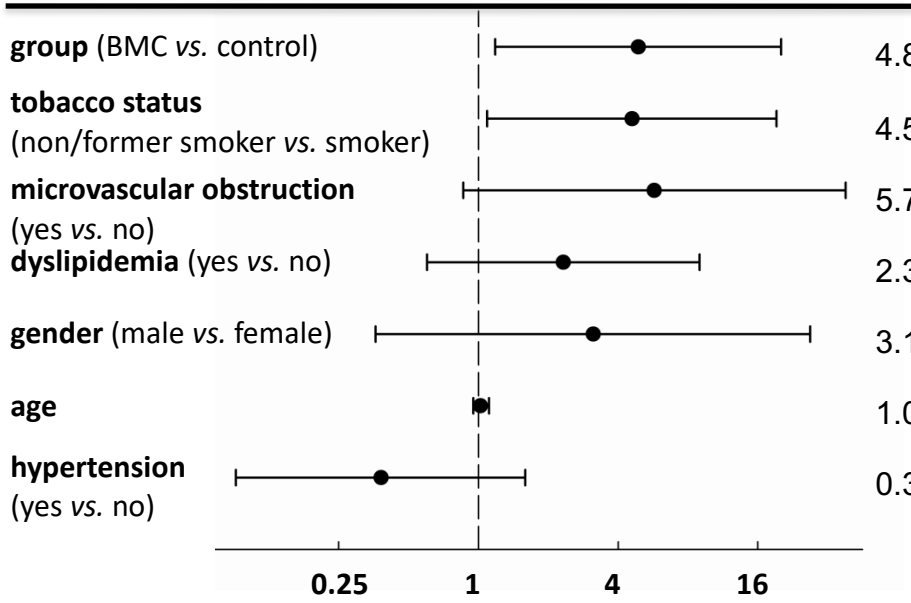
- Prespecified criterion of cell therapy success = 2 non viable segments become viable 3 months after myocardial infarction

- The number of patients with **myocardial viability improvement ≥2/17** was **twice greater in the BMC group**



RESULTS: Assessment of Cell Therapy Success (2)

Multivariate analysis



Significant role of smoking at the time of myocardial infarction

CONCLUSION

- The BONAMI trial is the first randomized multicenter trial to investigate the beneficial effect of coronary injection of autologous BMC on myocardial viability as a primary endpoint.

- In this trial, coronary autologous BMC injection, 9 days after acute MI, to patients with low EF, failed to reach the primary endpoint, although a strong trend was observed.

- The trend to improve myocardial viability was associated with a specific negative role of tobacco and positive role of no-reflow.

MISE EN PLACE DE L'ESSAI

Dec 2002	PHRC local	40 sujets	Fev 2003	13 000 €
Fev 2003	CCPPRB	40 sujets		favorable
Mai 2003	**PHRC nat.**	80 sujets	dec 2003	**219 000€**
Avril 2004	**Afssaps**	100 sujets	juil 2004	**favorable**
Sept 2004	**CCPPRB**	100 sujets		**favorable**

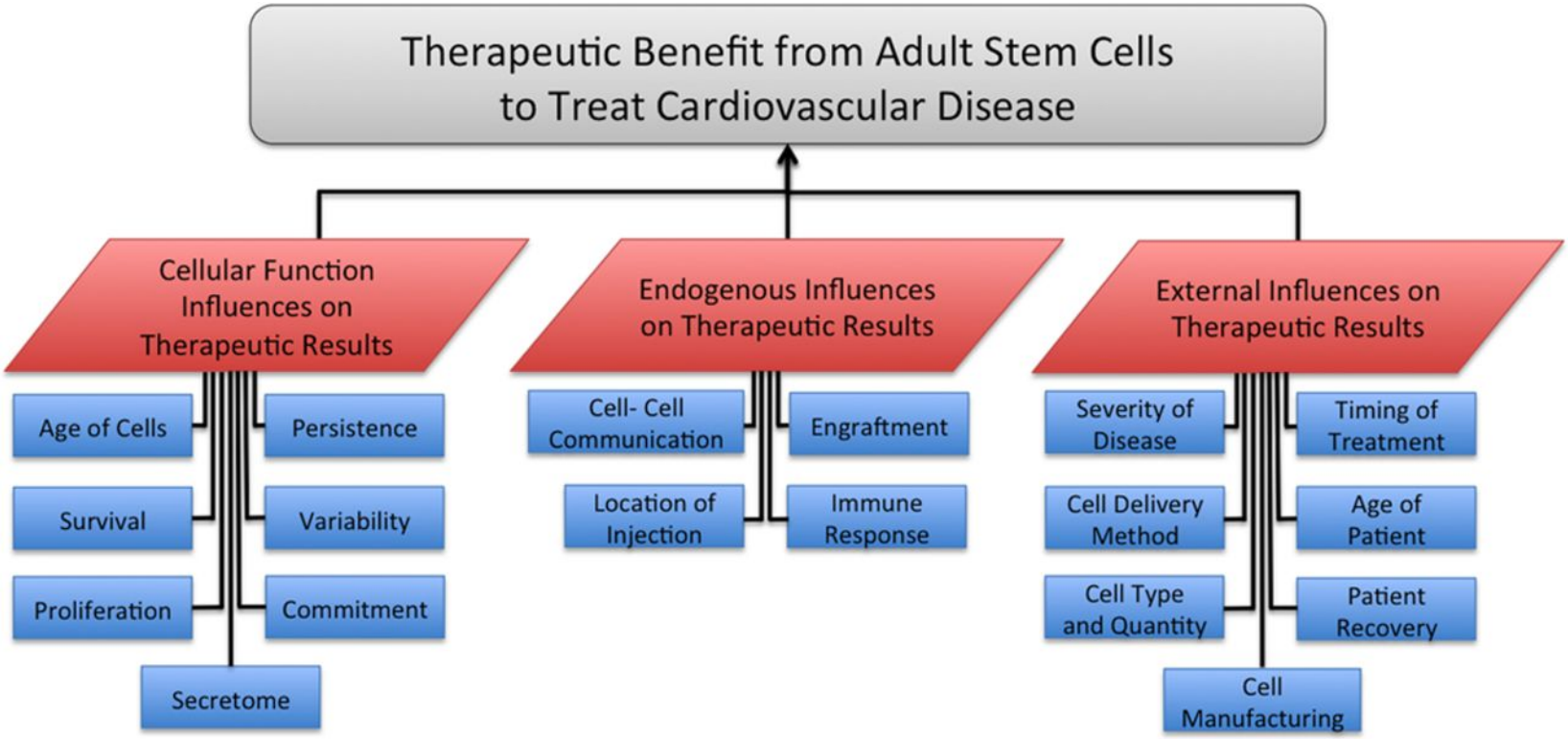
+ demandes de financements complémentaires (AFM, Fondation de France).

Début des inclusions: décembre 2004
janvier 2007: 100/100 patients inclus
Premiers résultats cliniques: fin-2010

Why proceed clinically while basic questions are unresolved?

- Use of stem cells for cardiac repair not yet ready for clinical application outside a research or trial setting
- Preclinical studies will not answer complex questions
- Trials provide some answers to preconceived hypothesis but also generate new questions
- Need for a large clinical trial to evaluate clinical endpoints

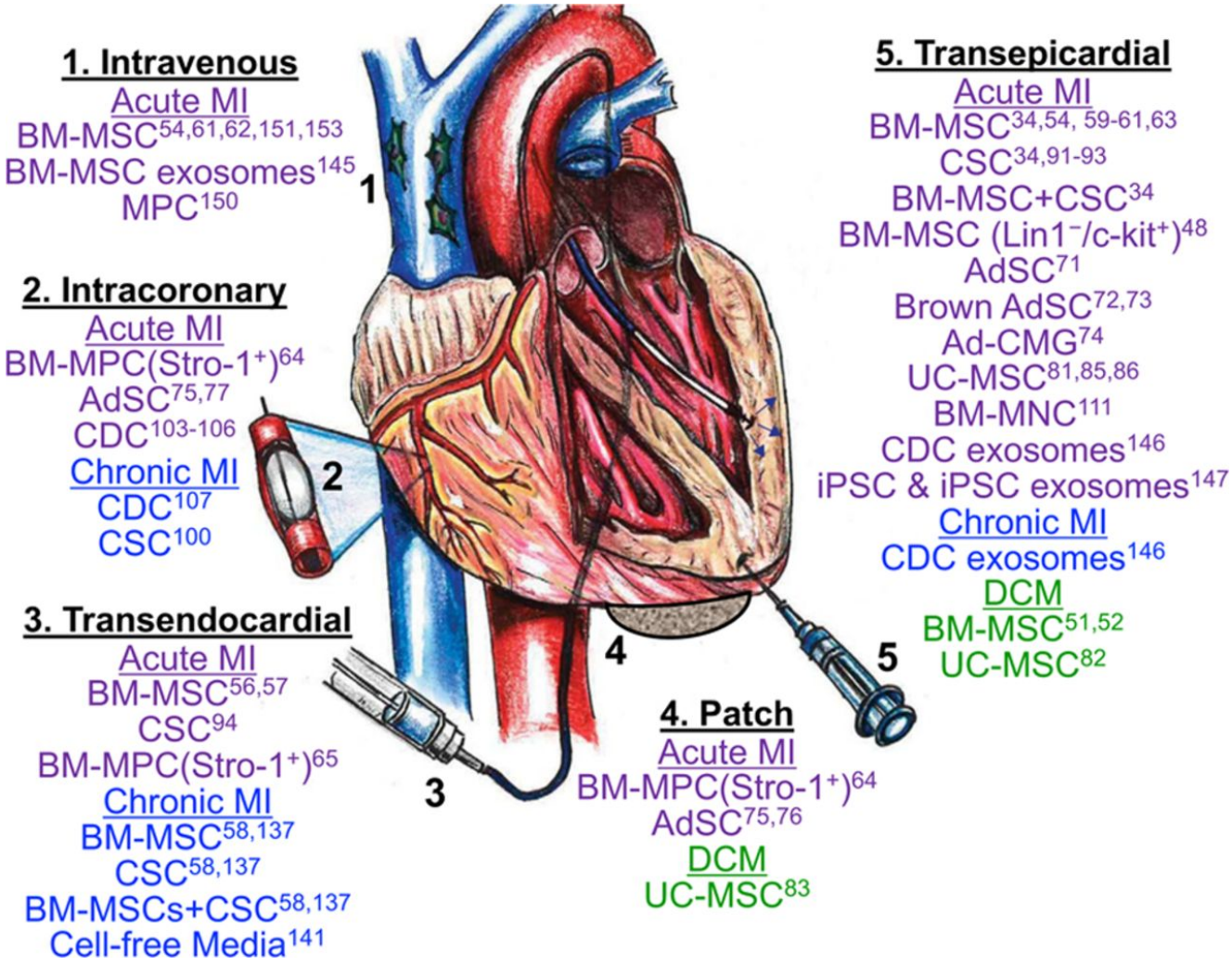
Factors influencing therapeutic outcomes when using stem cells.



Kathleen M. Broughton, and Mark A. Sussman Circ Res. 2016;118:867-880

American Heart Association.

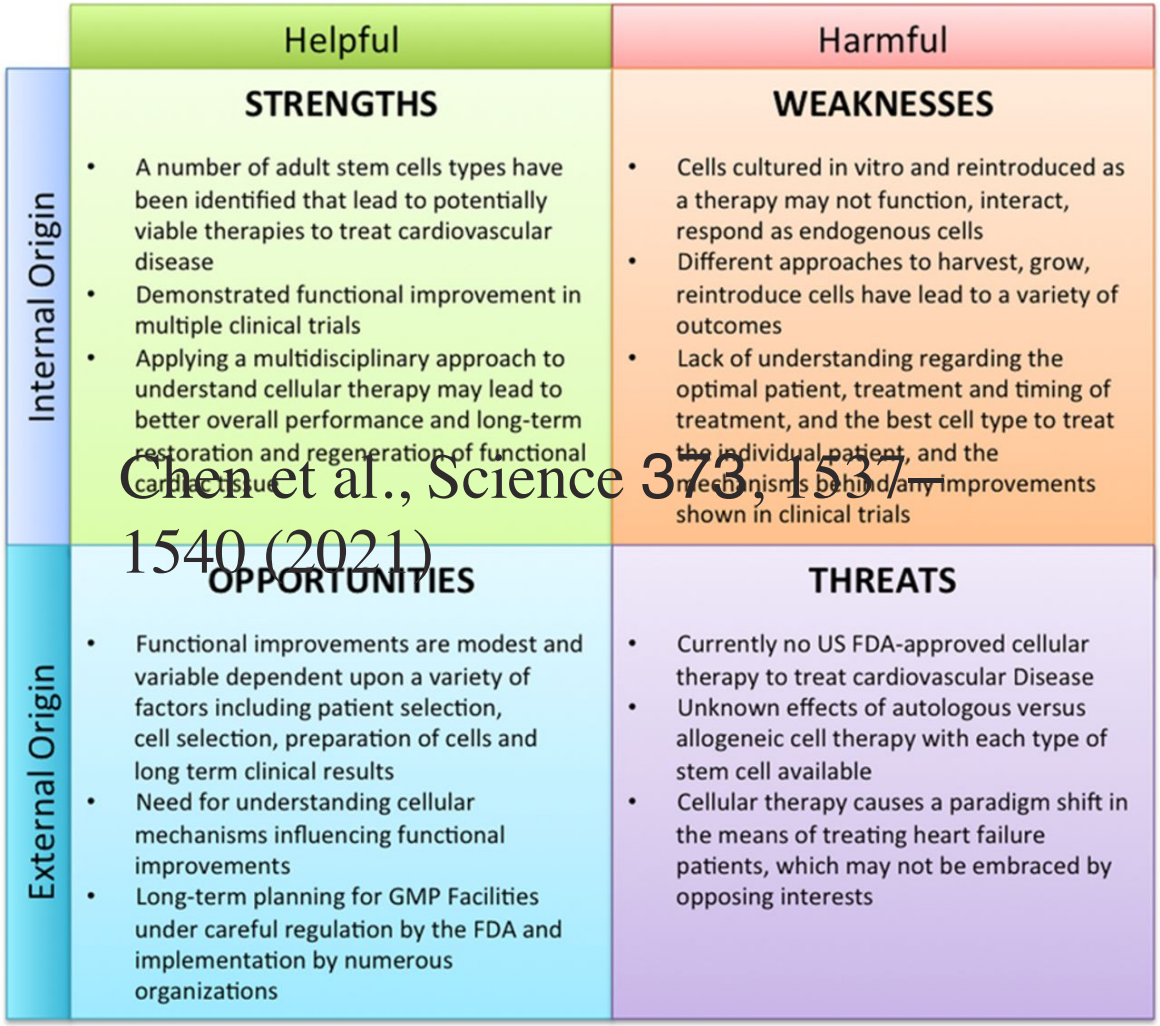
Different administration routes and cell types for the treatment of heart disease.



Bryon A. Tompkins et al. Circ Res. 2018;122:1006-1020

American Heart Association.

Strengths, Weaknesses, Opportunities, and Threats (SWOT) analysis of adult stems cells as a cardiovascular therapy.



Chen et al., Science 373, 1537–1540 (2021)

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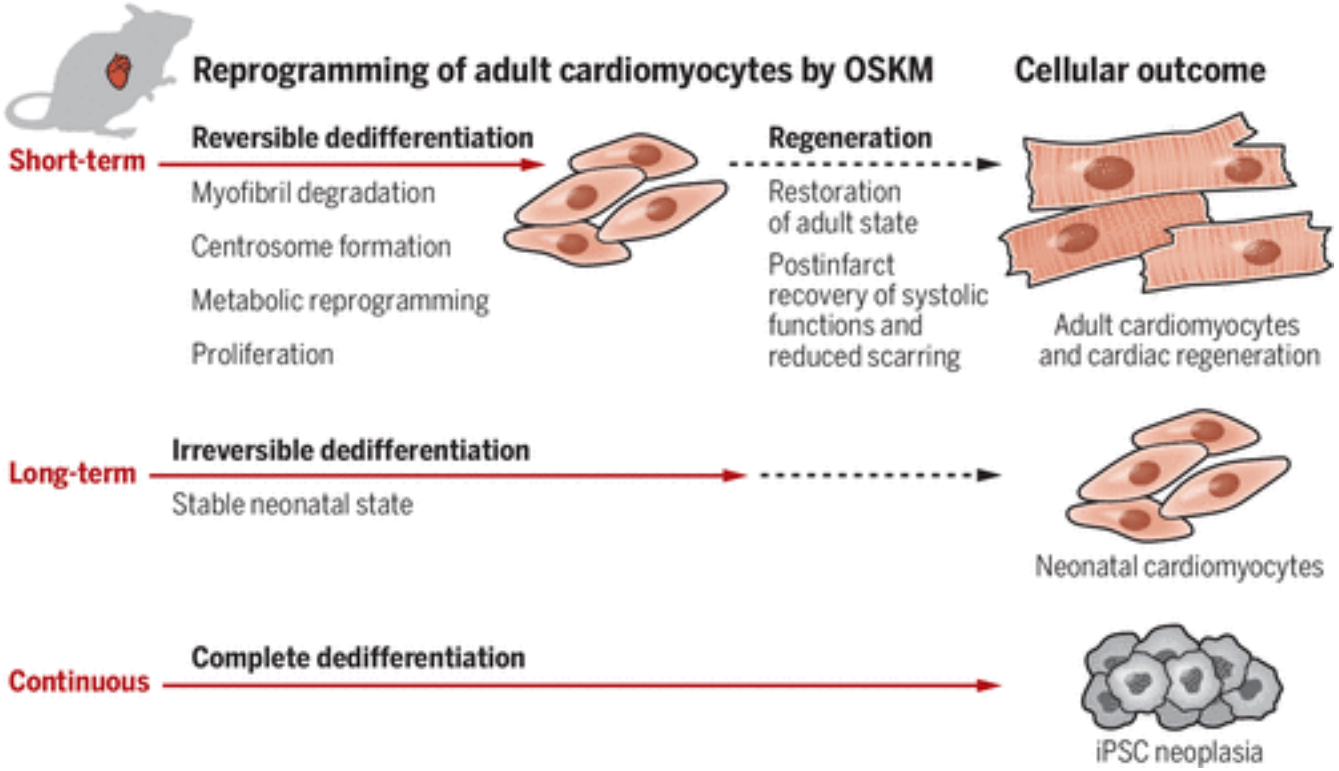
OSKM as a therapy

Reprogramming of adult cardiomyocytes in mice

The timing of in vivo reprogramming by *Oct4* (octamer-binding protein 4), *Sox2* (SRY-box 2), *Klf4* (Kruppel-like factor 4), and *Myc* (collectively, OSKM) in adult mouse cardiomyocytes is key to the outcome. Prolonged OSKM expression in vivo led to neonatal cardiomyocytes that could not mature or to neoplasias formed from induced pluripotent stem cells (iPSCs) within the heart, whereas short-term induction enabled adult cardiomyocytes to regenerate the heart.



Reversing aging for heart repair, Volume: 373, Issue: 6562, Pages: 1439-1440, DOI: (10.1126/science.abl8679)

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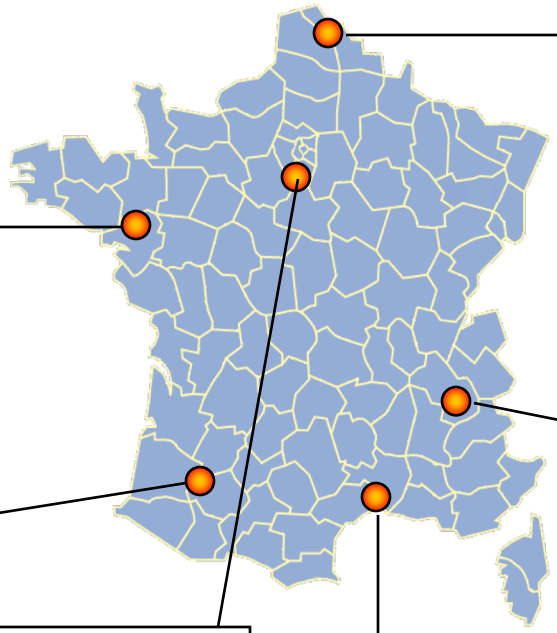

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