29èmes Journées Nationales d'Etude et de Perfectionnement de l'UNAIBODE - METZ
24/05/2012

ECOLE DE CHIRURGIE - NANCY LORRAINE

THERAPIE CELLULAIRE CARDIAQUE

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CELL & TISSUE THERAPY : New Therapeutic Strategy

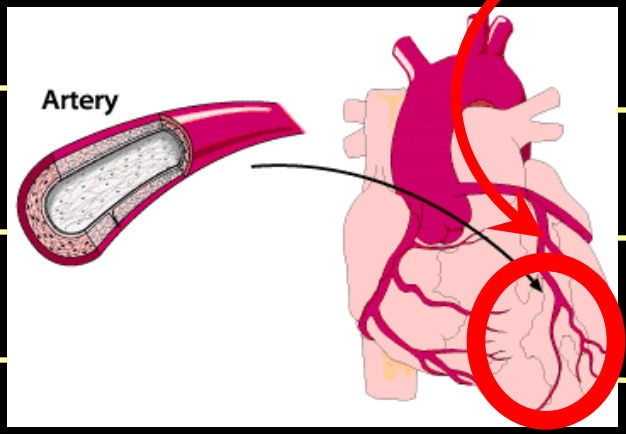
Myocardial Infarction

↓Angiogenesis

↓Cardiomyocytes

↑Fibrosis

↓Cardiac Function



Cell Therapy

↑Angiogenesis

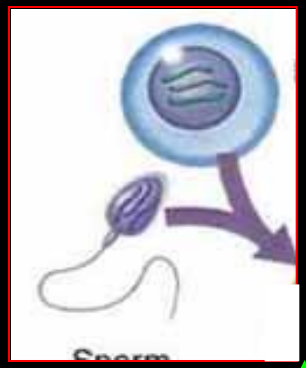
↑Cardiomyocytes

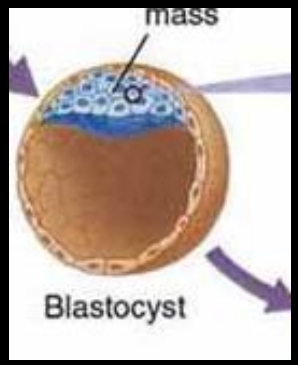
↓Fibrosis

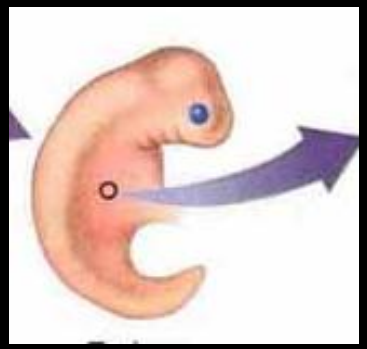
↑Cardiac Function

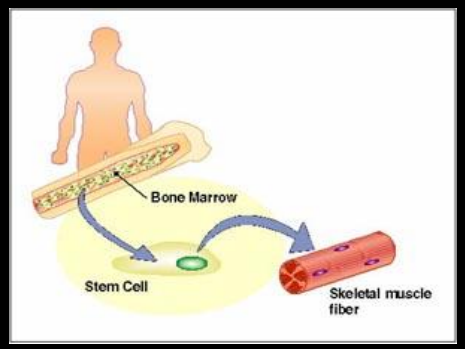
Inefficiency of Conventional therapy !
Incidence (USA): 500000cases/year

Cell Therapy: What cell?









Totipotent → Pluripotent → Multipotent

Clonage

embryon ← → adult

Unlimited number
High plasticity

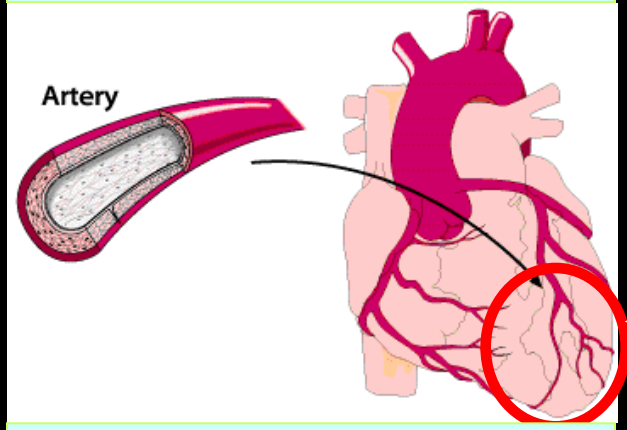
Limited number
Low plasticity

Long R&D

Rapid R&D

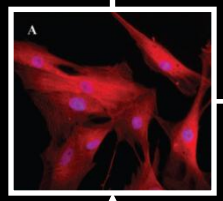
CELL & TISSUE THERAPY With BMSCs : Current Therapeutic Concept

Ischemic Heart Failure



Public Health Problem
Mortality: 7 millions/year

RECRUITMENT
Inflammatory
Chemokines
(SDF-1)



VSELs
Oct-4/Nanog
Rex1/Rif-1
AESS-1/Dppa1
(pluripotent)

Cardiogenesis
?
Angiogenesis
?

MSCs
CD34-/CD45-
CD90+/CD29+
CD105+/CXCR4+
(multipotent)

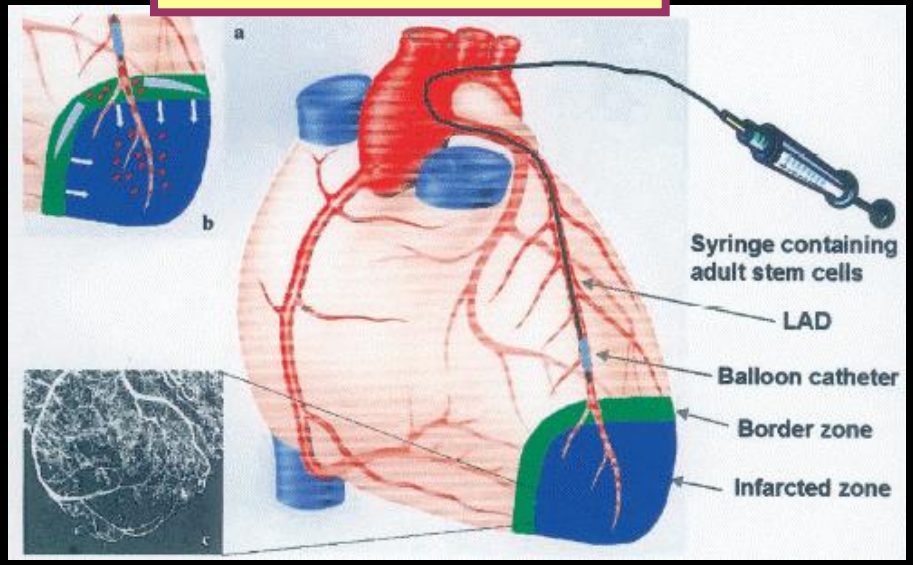
Cardiogenesis
GATA-4
Nkx2.5/Csx
MEF2C
Angiogenesis
Angiopoïetin1/Akt

Circulating EPs
CD34+/c-kit+
CD31+/CD133+
CXCR4+

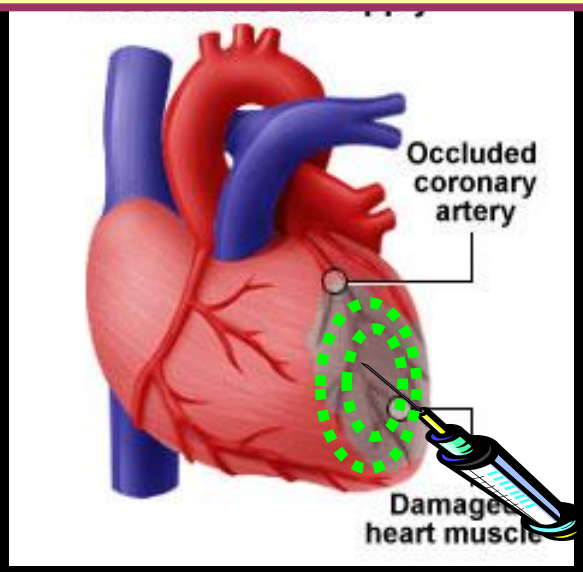
Cardiogenesis
GATA-4
Nkx2.5/Csx
MEF2C

CCT IN CLINICAL INVESTIGATION – WAYS OF CELL IMPLANTATION

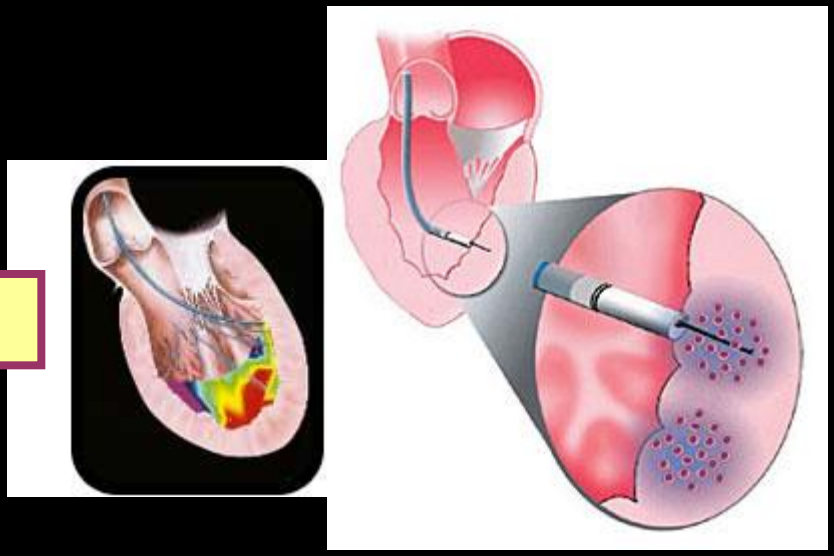
Intracoronary



Trans-epicardial

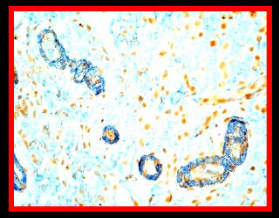


Trans-endocardial



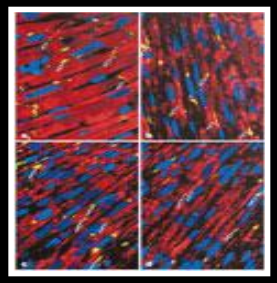
Cardiac cell therapy (CCT) – preclinical results

Angiogenesis



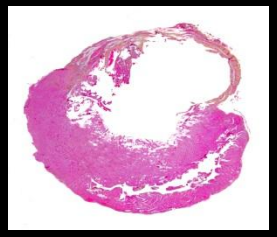
Kocher et al., Nat. Med., 7 : 430-436, 2001 ;
Kinnaird et al., Circ. Res., 94 : 678-685, 2004

Cardiogenesis



Orlic et al., Nature, 410:701-705, 2001
Kajstura et al., Circ. Res., 96 : 127-137, 2005

LV remodeling



Kudo et al., J. Mol. Cell. Cardiol., 35 : 1113-1119, 2003
Xu et al., Coron Artery Dis, 16: 445-455, 2005

Cardiac function

Mangi et al., Nat. Med., 9 : 1195-1201, 2003
Thomson et al., J Heart Lung Transplant, 24: 205-214, 2005

VERY PROMISSING PRE-CLINICAL OUTCOMES !!!

CCT – RANDOMIZED STUDIES – INTRACORONARY INJECTION

Table 1. Randomized, Controlled Trials of BMC for Cardiac Disease.*

Trial or Investigator Group	Setting	Design	No. of Cells Administered in Treatment Group	Results	
BOOST[4,9]	PCI after acute myocardial infarction	Randomized trial 30 patients received BMC; 30 received no infusion LVEF assessed by MRI	Approximately 2.5×10^9 unfractionated BMC	At 6 mo: LVEF 6% greater in BMC group than in control group At 18 mo: no significant difference in LVEF between the 2 groups	+
Janssens et al.[8]	PCI after acute myocardial infarction	Randomized, double-blind trial 33 patients received BMC; 34 received placebo infusion LVEF was assessed by MRI	Approximately 3×10^8 Ficoll-separated BMC	At 4 mo: no significant difference in overall LVEF; decreased infarct size and better regional function in BMC group	=
TOPCARE-CHD[6]	Chronic left ventricular dysfunction	Randomized, crossover trial In the second phase, 24 patients received CPC, 28 received BMC, 23 received no infusion LVEF assessed by left ventricular angiography	Approximately 2×10^8 Ficoll-separated BMC or approximately 2×10^7 Ficoll-separated, cultured CPC	At 3 mo: greater increase in LVEF (2.9 percentage points) in BMC group than in CPC group or control group	+
ASTAMI[7]	PCI after acute myocardial infarction	Randomized trial 47 patients received BMC; 50 received no infusion LVEF assessed by SPECT, echocardiography, and MRI	Approximately 7×10^7 Ficoll-separated BMC	At 6 mo: no significant difference in LVEF between the 2 groups	=
REPAIR-AMI[5]	PCI after acute myocardial infarction	Randomized, double-blind trial 101 patients received BMC; 98 received placebo infusion LVEF assessed by left ventricular angiography	Approximately 2.4×10^8 Ficoll-separated BMC	At 4 mo: greater absolute increase in LVEF in BMC group than in placebo group (5.5% vs. 3.0%) At 1 yr: reduction in combined adverse clinical events in BMC group as compared with placebo group	+

CONTRADICTORY AND NOT RELEVANT OUTCOMES !!!!

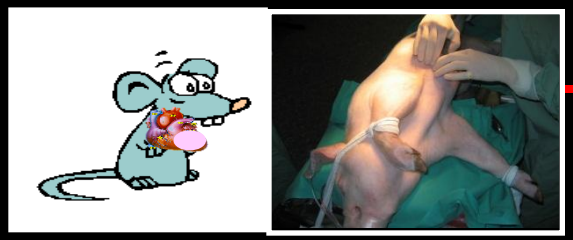
Cardiac Cell Transplantation in NANCY

NANCY GROUP

R & D

- Animal model (Rat, Pig)
- CSMM characterization
- Cell tracking
- Histology

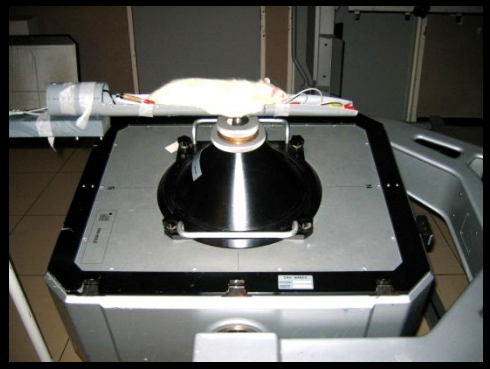
Preclinical evaluation – Clinical Criteria

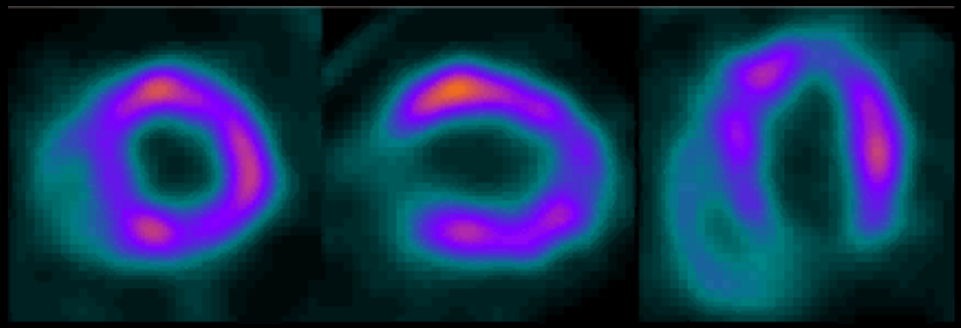


SPECT, PETSCAN

- MI Diagnostics
- In vivo Cell/lesion co-localization
- Impact of cell therapy

CARDIAC CELL THERAPY-GATED SPECT

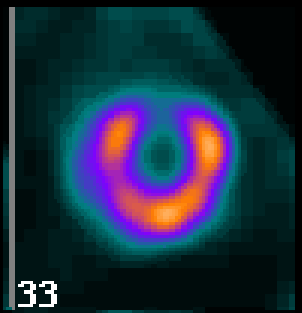


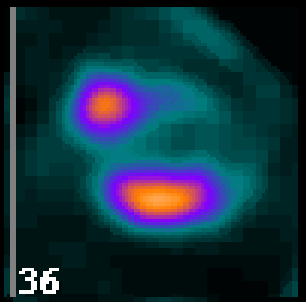


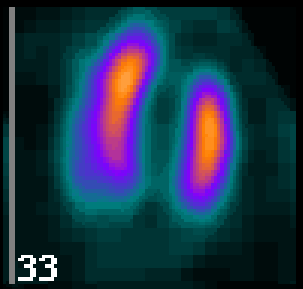
Short axis
médian

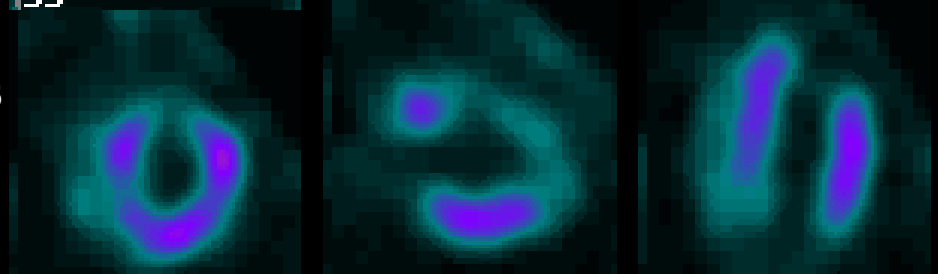
Long Axis
vertical

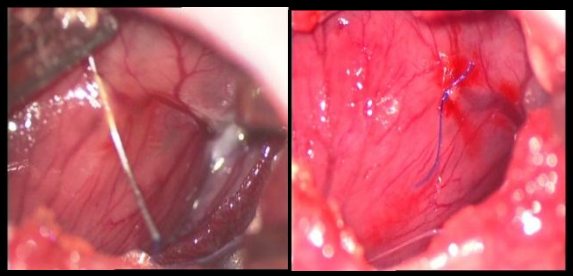
Long Axis
horizontal



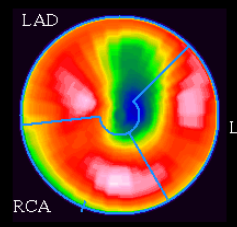








Perfusion



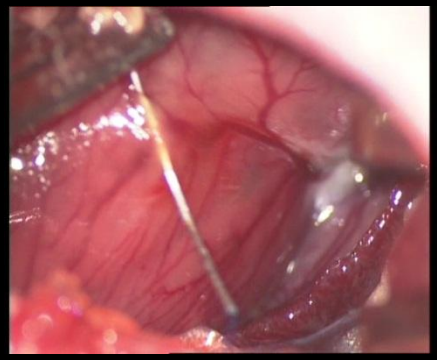
infarct size : 23%
(area <50%)

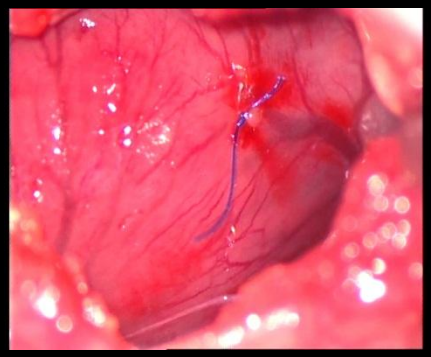
ED vol : 0.600 ml
ES vol : 0.320 ml
LVEF : 47 %

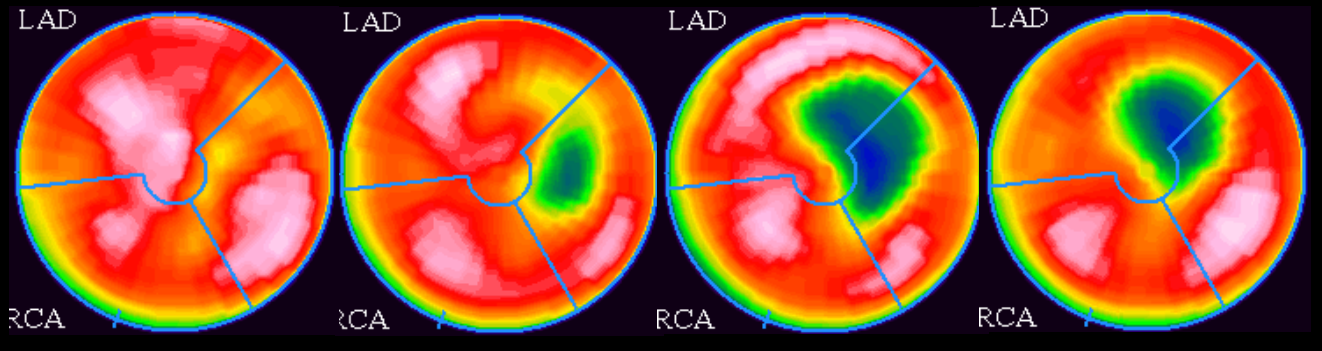
Vanhove et al., *Eur JNM*, 2005
Maskali, Franken, Poussier, Tran, *JNM*, 2006
Poussier, Makali, Tran, JNM, 2009

MI = HIGH VARIABILITY!!!!

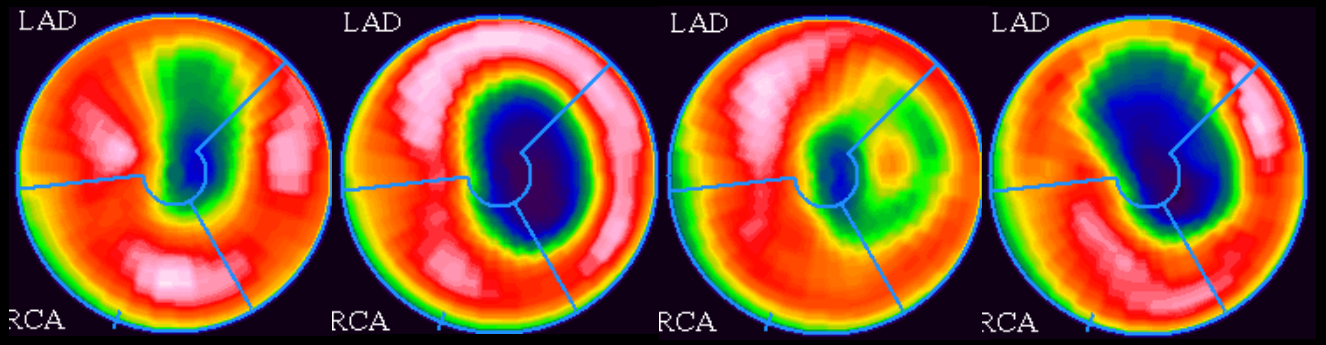
Coronary ligation







8% 23% 37% 37%

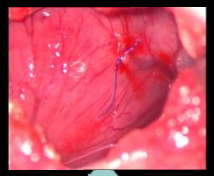


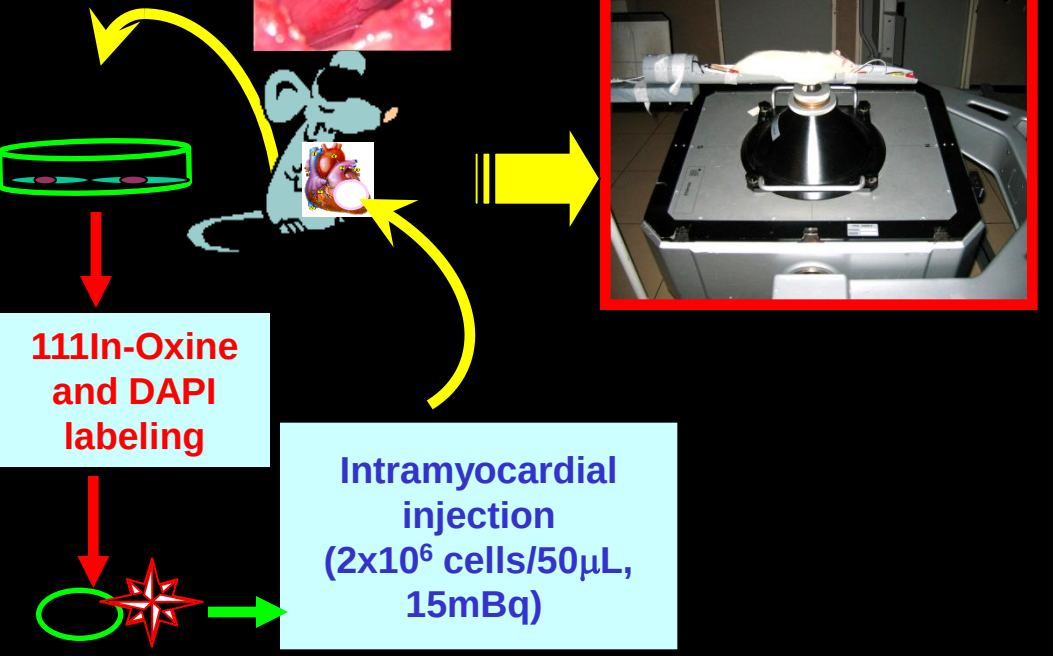
42% 47% 47% 52%

Maskali, Franken, Poussier, Tran, et al., *JNM*, 2006

CELL LOCATION (Tc/In SPECT ACQUISITION)

Coronary ligation

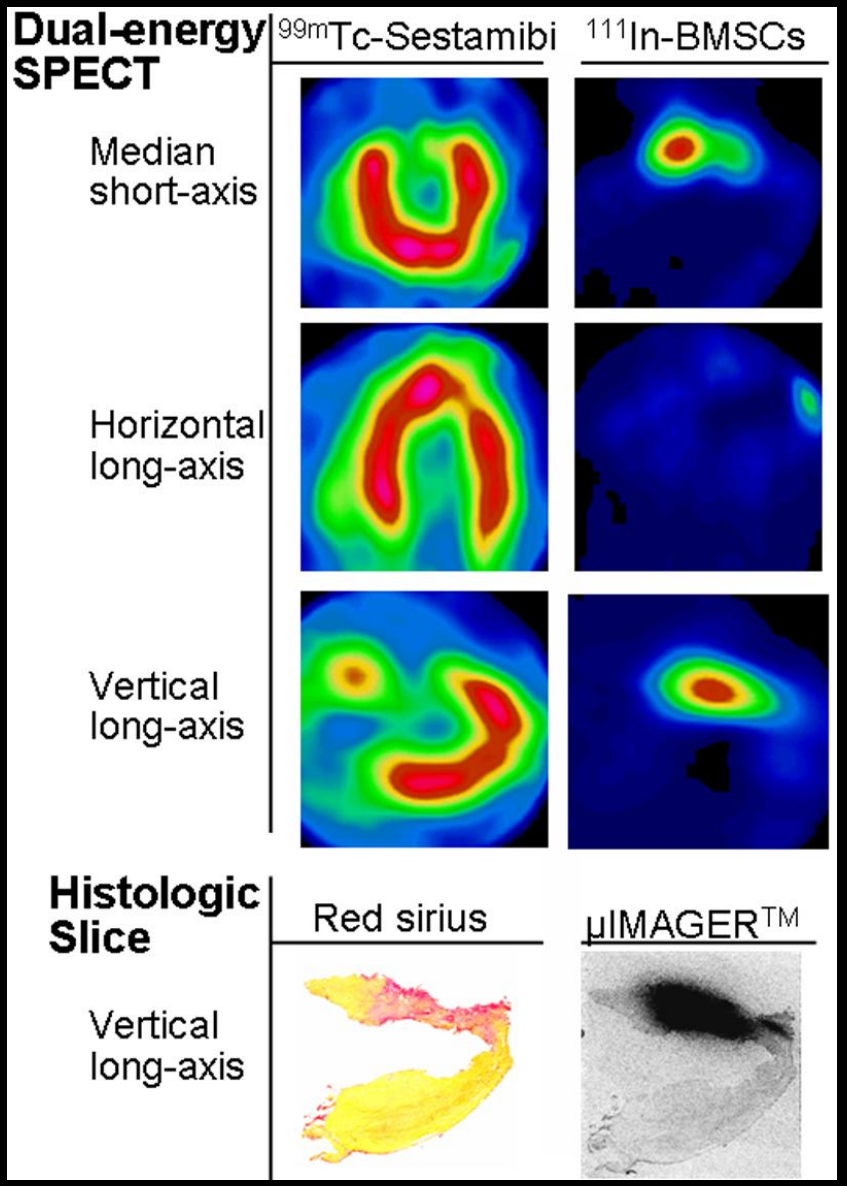




111In-Oxine and DAPI labeling

Intramyocardial injection (2x10^6 cells/50µL, 15mBq)

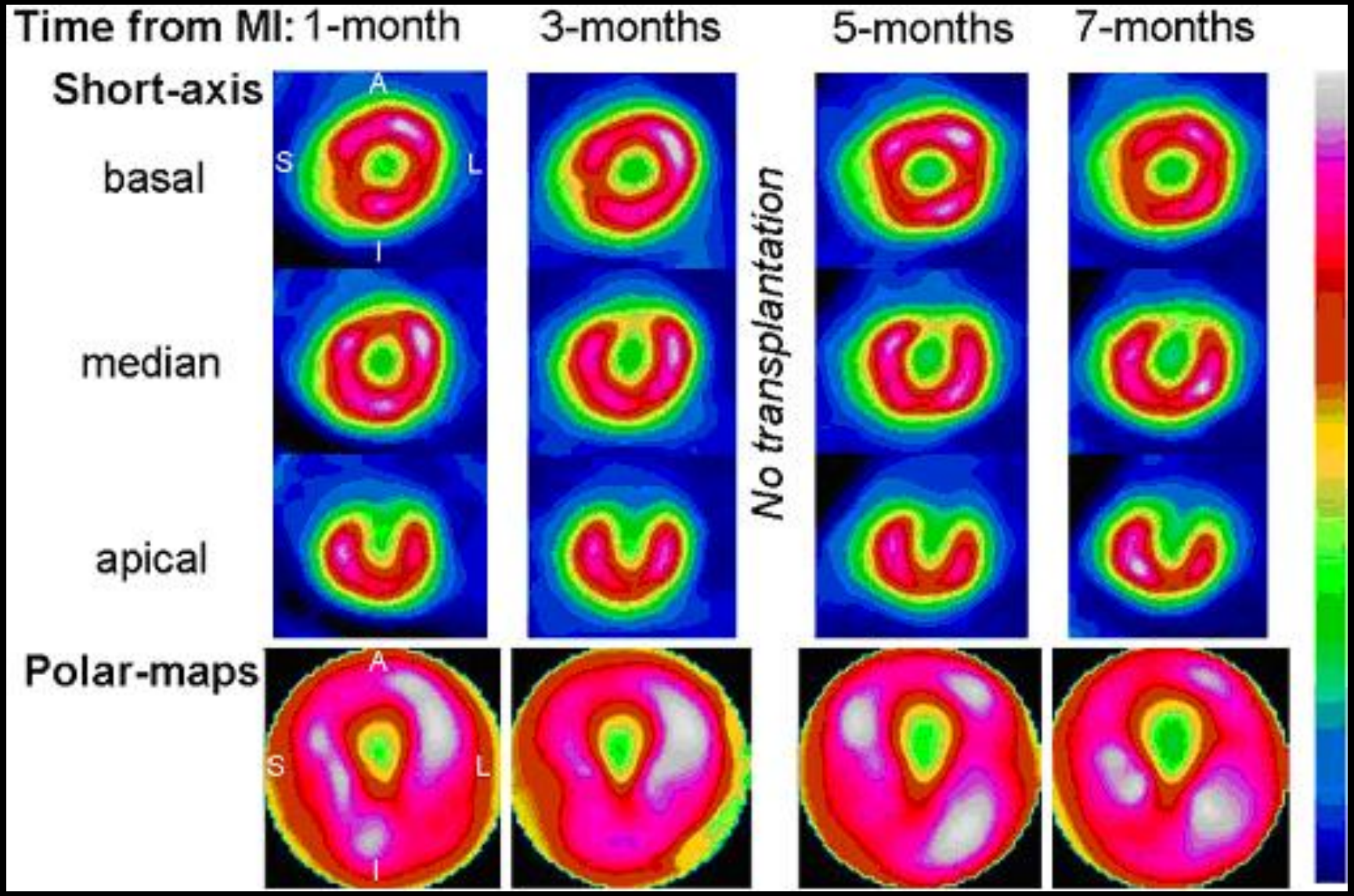
Dual SPECT TC/In



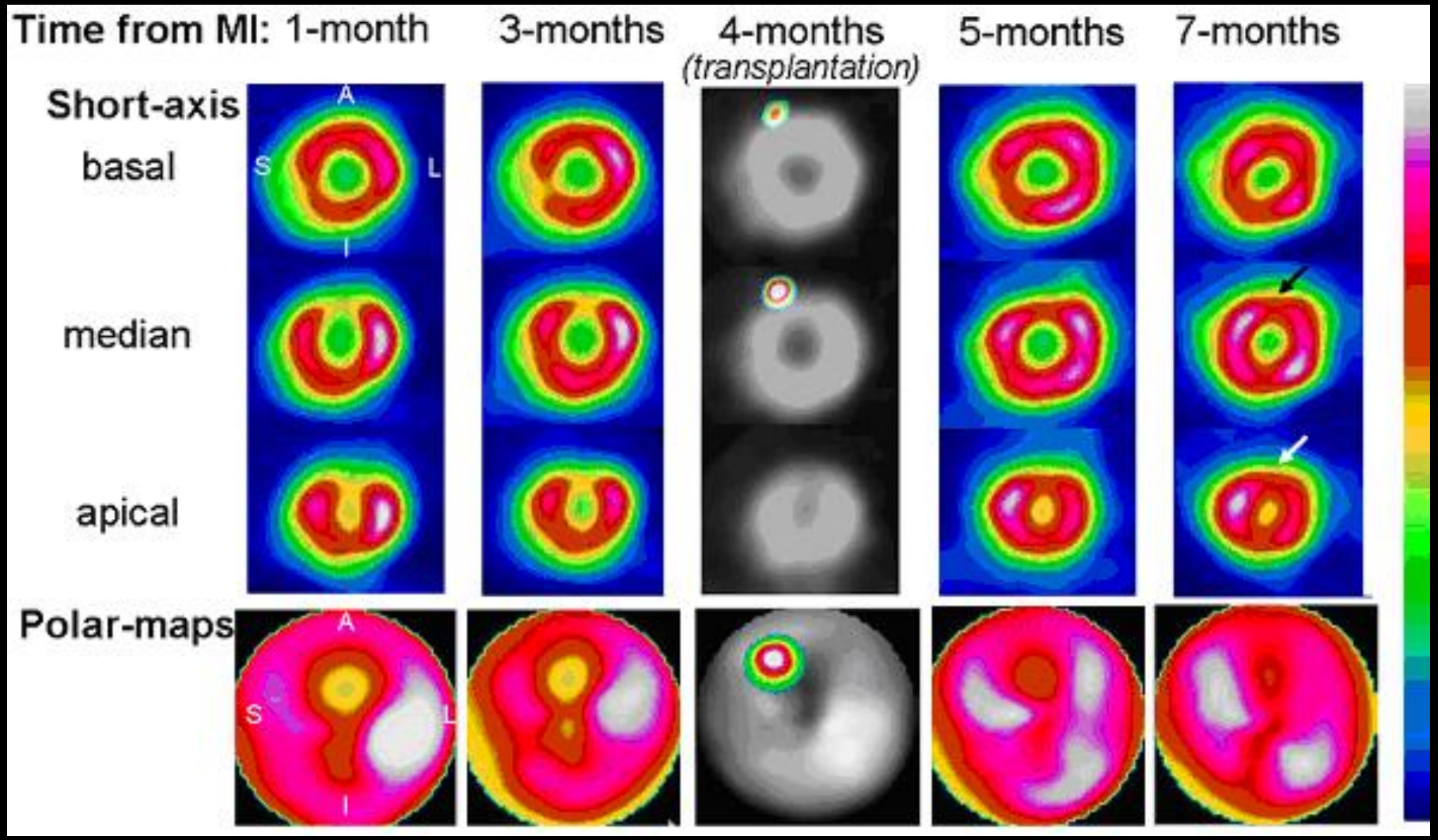
Tran et al., *Cell Transplant*., 2006

Maskali, Poussier, Marie, Tran, et al., *J Nucl Cardiol*, 2005

Impact of CT (1)

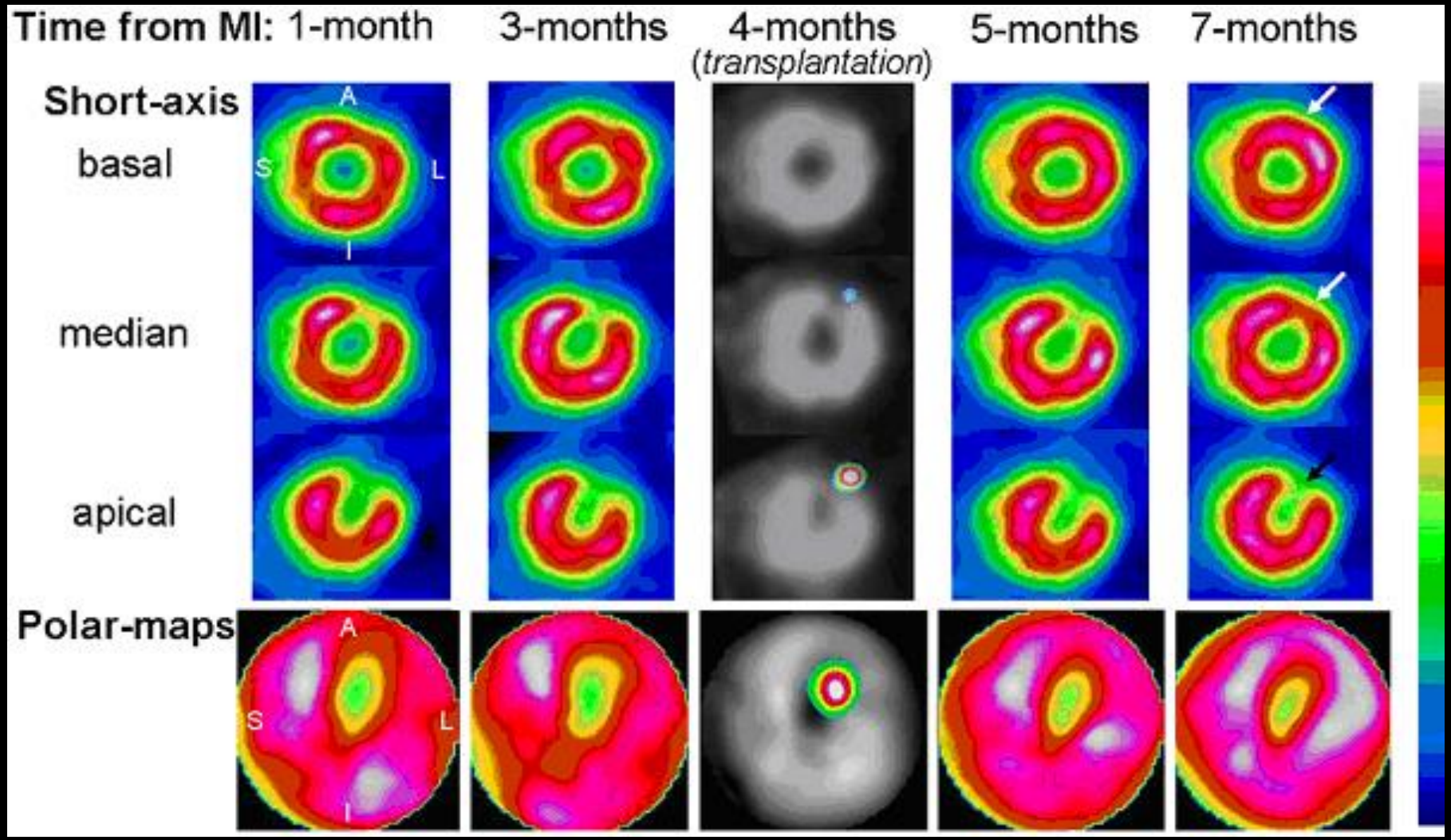


Impact of CT (2)



Tran et al., *JNM*., 48: 405-412, 2007

Impact of CT(3)



Tran et al., *JNM.*, 48: 405-412, 2007

Clinical Phase (2006-2009)

14 patients (Chronic MI)
CABG indication presenting necrotic MI areas

Pre-therapeutic status
IRM
PET-FDG & gated-SPECT
Echocardiography,…

Randomisation

Untreated group
Revascularisation
(n = 7)

Treated group
Revascularisation + cell therapy (n = 7)

SURGICAL PROCEDURE

Echocardiography (1 Wk)

Gated-SPECT (1 mo)

post-therapeutic status (3 mo)
IRM
PET-FDG & gated-SPECT
Echocardiography

Gated-SPECT (6 mo)

TIMING OF SURGICAL PROCEDURES

Time

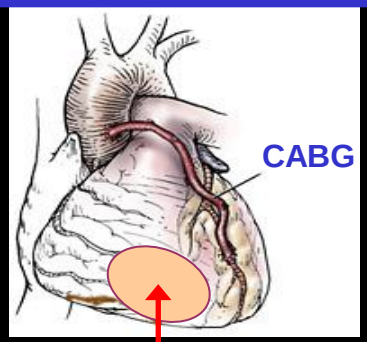
3H

Groupe Cell Therapy (n = 7)

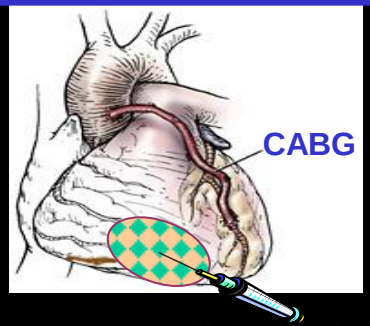
MNC harvest
(100 ml) (UTCT)

Selection- Cell preparation

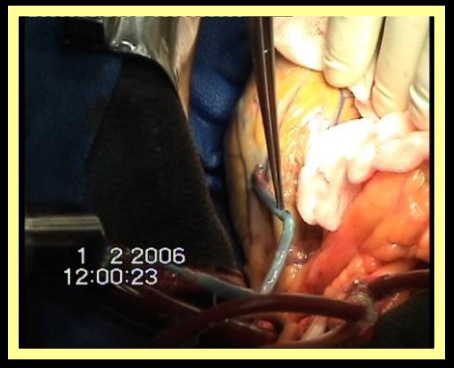
Surgical procedure of CABG

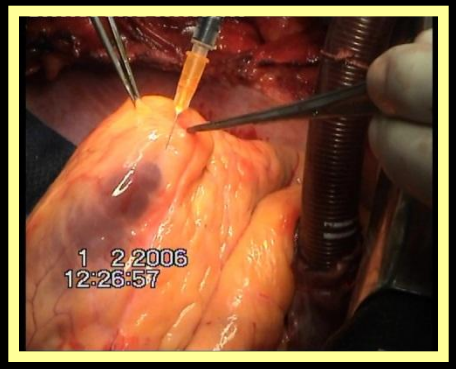


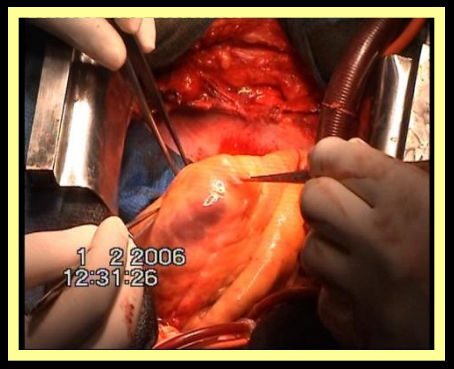
Infarct area



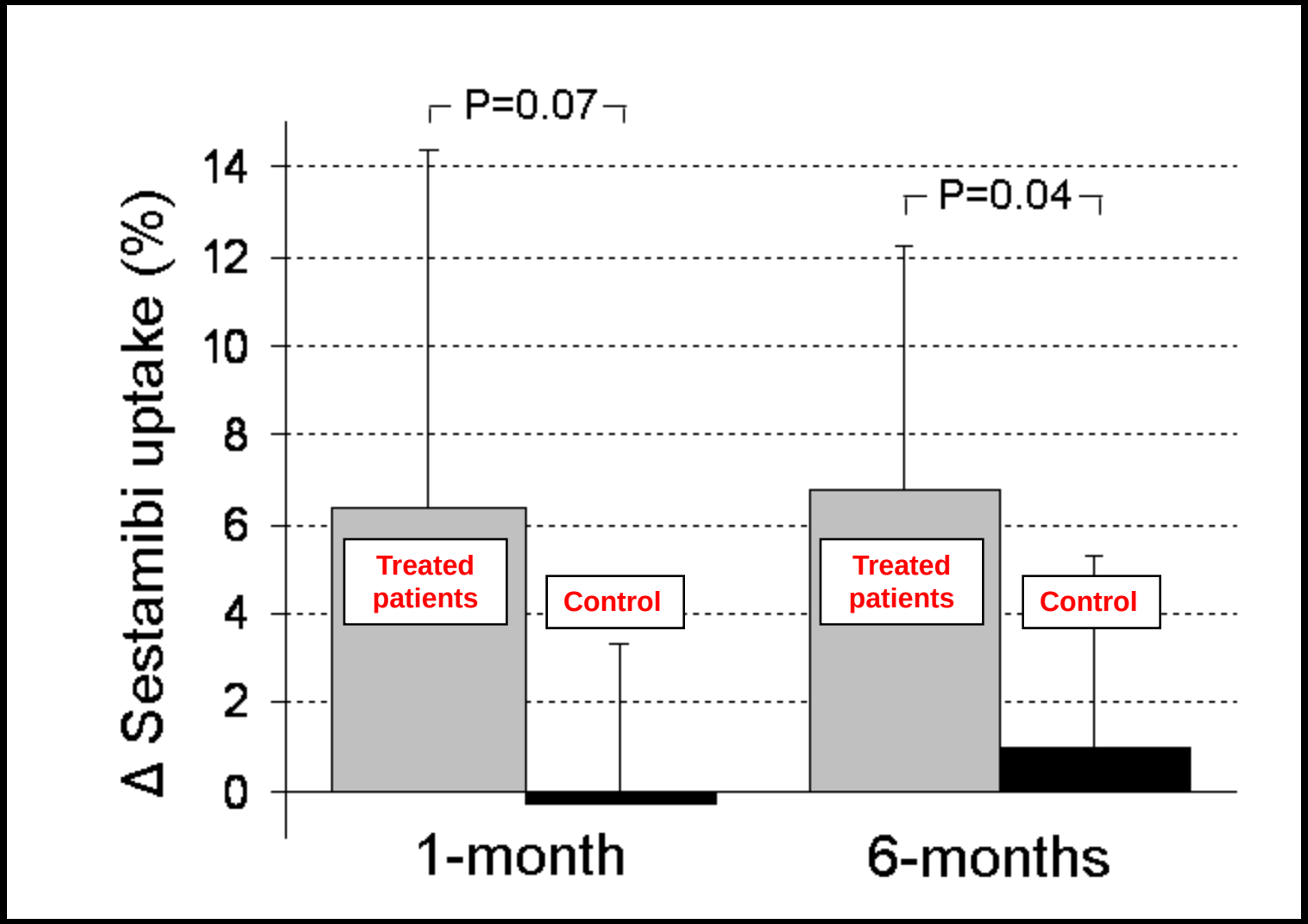
Intramyocardial injection
(20-40 injections; dans la zone infarcie)





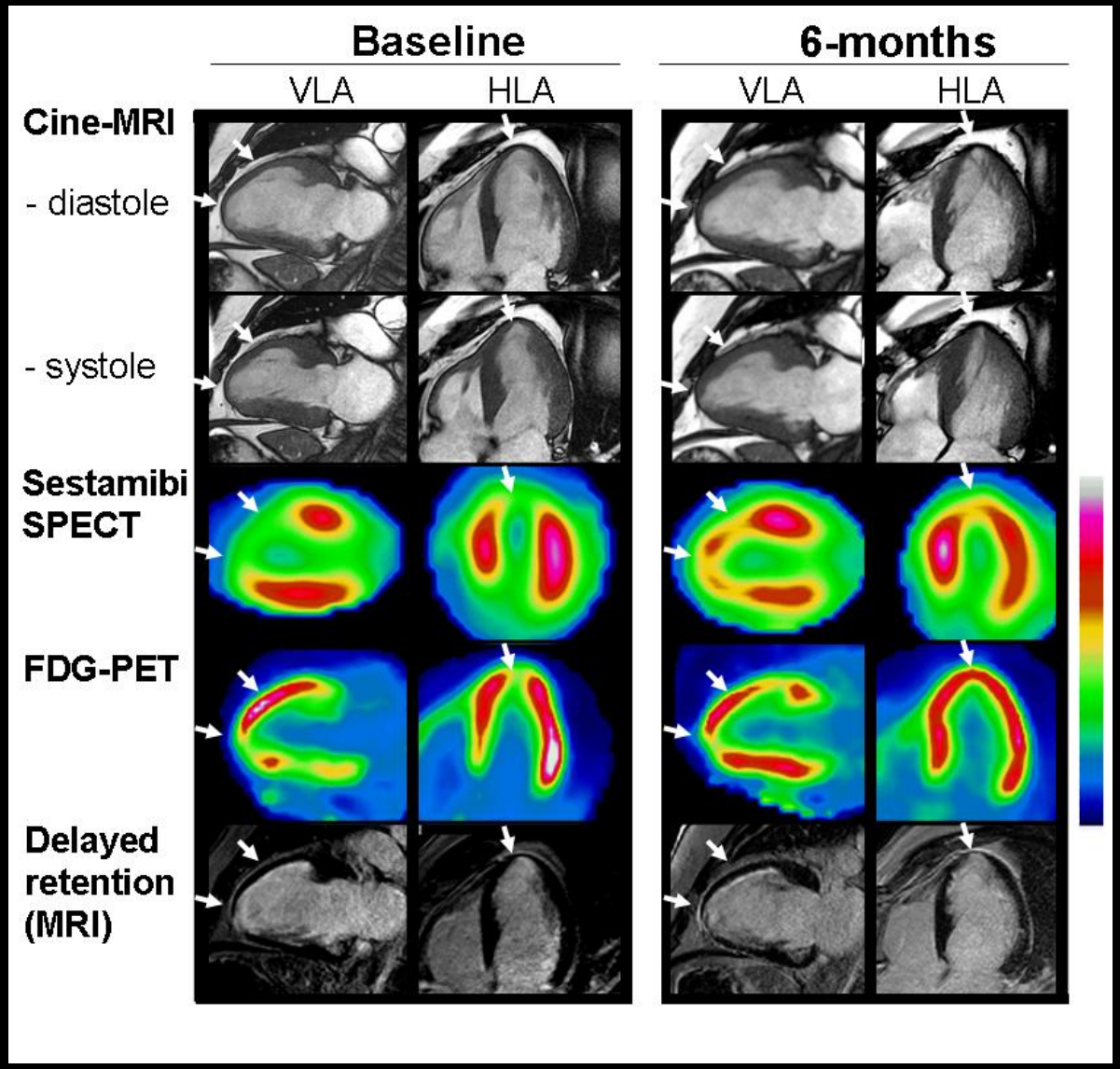


CARDIAC CELL THERAPY IN PERFUSION STATUS



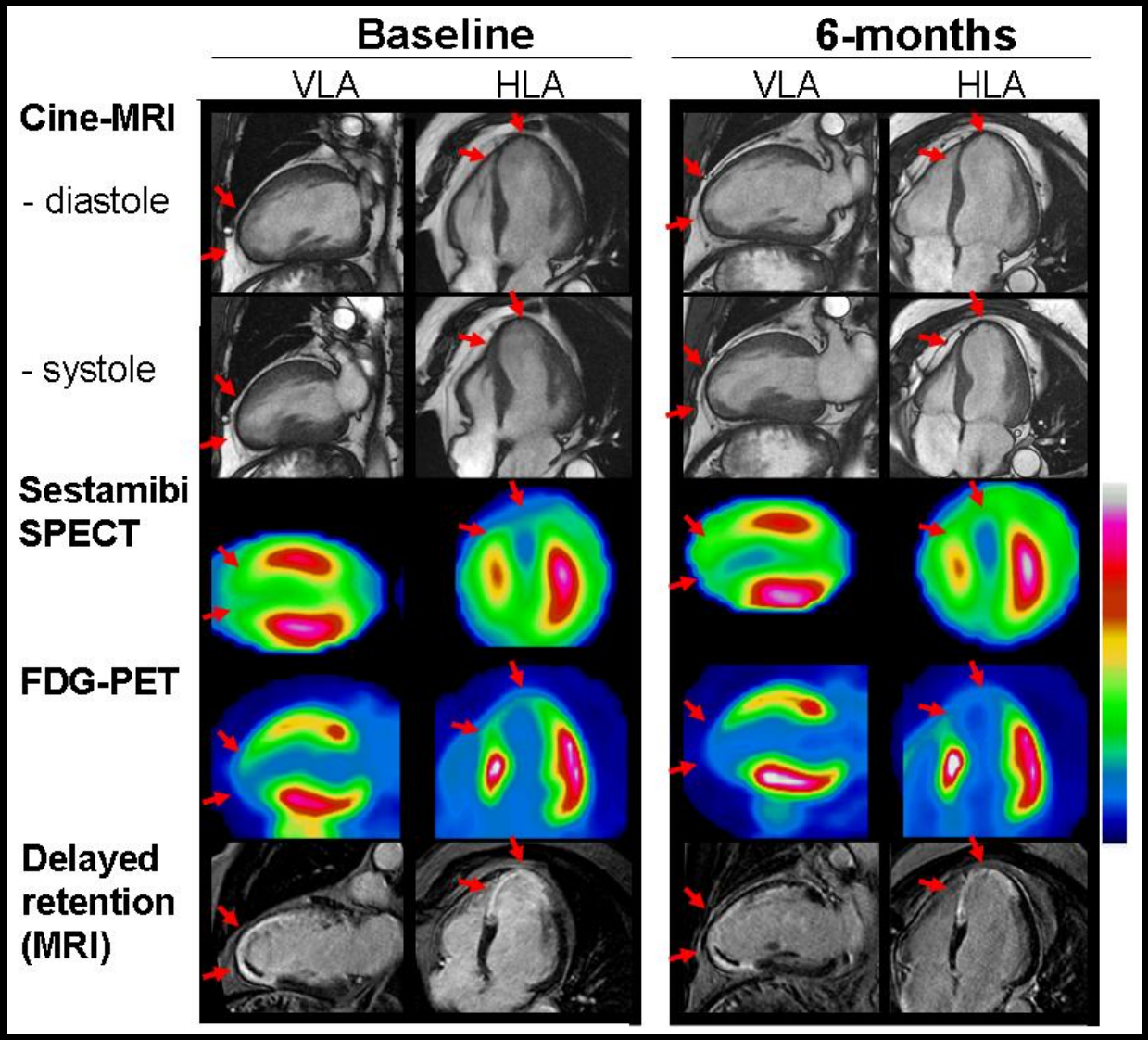
Maureira, Tran & Marie., *JNM*., in press 2012

CARDIAC CELL THERAPY IN VIABILITY & PERFUSION STATUS



Patient good responder = Existence of a residual ischemia!

CARDIAC CELL THERAPY IN VIABILITY & PERFUSION STATUS

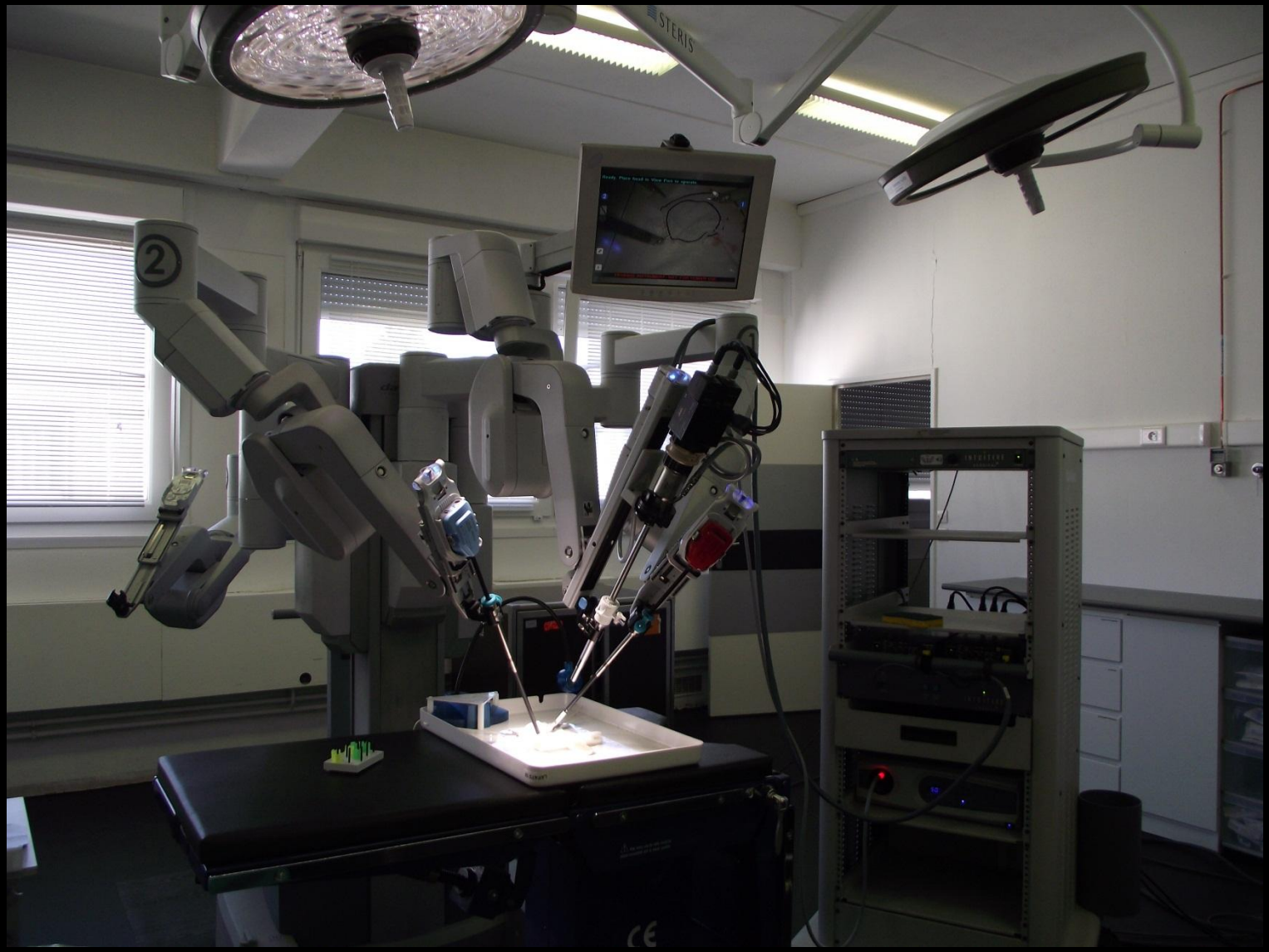


Patient non responder = NO residual ischemia!

SCHOOL OF SURGERY NANCY

MERCI

LIFE IN THE SCHOOL OF SURGERY



LIFE IN THE SCHOOL OF SURGERY