ECOLE DE CHIRURGIE - NANCY LORRAINE
THERAPIE CELLULAIRE CARDIAQUE

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Myocardial Infarction

↓Angiogenesis

↓Cardiomyocytes

↑Fibrosis

↓Cardiac Function

Cell Therapy

↑Angiogenesis

↑Cardiomyocytes

↓Fibrosis

↑Cardiac Function

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

CELL & TISSUE THERAPY: New Therapeutic Strategy
**Cell Therapy: What cell?**

**Totipotent**
- Unlimited number
- High plasticity
- Long R&D

**Pluripotent**
- Limited number
- Low plasticity

**Multipotent**
- Limited number
- Low plasticity
- Rapid R&D

**Clonage**
- embryo
  - Unlimited number
  - High plasticity
  - Long R&D
- adult
  - Limited number
  - Low plasticity
  - Rapid R&D
Ischemic Heart Failure

Public Health Problem
Mortality: 7 millions/year

RECRUITMENT
Inflammatory Chemokines (SDF-1)

Cell & Tissue Therapy With BMSCs: Current Therapeutic Concept

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
Angiopoietin1/Akt

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

Cardiogenesis
GATA-4
Nkx2.5/Csx
MEF2C
Intracoronary

Trans-epicardial

Trans-endocardial
Cardiac cell therapy (CCT) – preclinical results

Angiogenesis
  Kinnaird et al., Circ. Res., 94: 678-685, 2004

Cardiogenesis
  Kajstura et al., Circ. Res., 96: 127-137, 2005

LV remodeling
  Xu et al., Coron Artery Dis, 16: 445-455, 2005

Cardiac function
  Thomson et al., J Heart Lung Transplant, 24: 205-214, 2005

VERY PROMISSING PRE-CLINICAL OUTCOMES !!!
### Table 1. Randomized, Controlled Trials of BMC for Cardiac Disease.

<table>
<thead>
<tr>
<th>Trial or Investigator Group</th>
<th>Setting</th>
<th>Design</th>
<th>No. of Cells Administered in Treatment Group</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOOST^4,9</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized trial 30 patients received BMC; 30 received no infusion LVEF assessed by MRI</td>
<td>Approximately 2.5×10^9 unfractionated BMC</td>
<td>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</td>
</tr>
<tr>
<td>Janssens et al.^8</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized, double-blind trial 33 patients received BMC; 34 received placebo infusion LVEF was assessed by MRI</td>
<td>Approximately 3×10^8 Ficoll-separated BMC</td>
<td>At 4 mo: no significant difference in overall LVEF; decreased infarct size and better regional function in BMC group</td>
</tr>
<tr>
<td>TOPCARE-CHD^6</td>
<td>Chronic left ventricular dysfunction</td>
<td>Randomized, crossover trial In the second phase, 24 patients received CPC, 28 received BMC, 23 received no infusion LVEF assessed by left ventricular angiography</td>
<td>Approximately 2×10^8 Ficoll-separated BMC or approximately 2×10^7 Ficoll-separated cultured CPC</td>
<td>At 3 mo: greater increase in LVEF (2.9 percentage points) in BMC group than in CPC group or control group</td>
</tr>
<tr>
<td>ASTAMI^7</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized trial 47 patients received BMC; 50 received no infusion LVEF assessed by SPECT, echocardiography, and MRI</td>
<td>Approximately 7×10^7 Ficoll-separated BMC</td>
<td>At 6 mo: no significant difference in LVEF between the 2 groups</td>
</tr>
<tr>
<td>REPAIR-AMI^5</td>
<td>PCI after acute myocardial infarction</td>
<td>Randomized, double-blind trial 101 patients received BMC; 98 received placebo infusion LVEF assessed by left ventricular angiography</td>
<td>Approximately 2.4×10^8 Ficoll-separated BMC</td>
<td>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</td>
</tr>
</tbody>
</table>

**CONTRADICTORY AND NOT RELEVANT OUTCOMES !!!!**
Cardiac Cell Transplantation in NANCY

Preclinical evaluation – Clinical Criteria

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

NANCY GROUP

SPECT, PETSCAN
- MI Diagnostics
- In vivo Cell/lesion co-localization
- Impact of cell therapy
CARDIAC CELL THERAPY - GATED SPECT

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

infarct size : 23%  
(area <50%)
ED vol : 0.600 ml
ES vol : 0.320 ml
LVEF : 47%
Coronary ligation

MI = HIGH VARIABILITY!!!!

8%  23%  37%  37%

42%  47%  47%  52%

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

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

CELL LOCATION (Tc/In SPECT ACQUISITION)

Coronary ligation

111In-Oxine and DAPI labeling

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

Dual SPECT TC/In

Dual-energy SPECT

<table>
<thead>
<tr>
<th>99mTc-Sestamibi</th>
<th>111In-BMSCs</th>
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</thead>
<tbody>
<tr>
<td>Median short-axis</td>
<td></td>
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<tr>
<td>Horizontal long-axis</td>
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<tr>
<td>Vertical long-axis</td>
<td></td>
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</tbody>
</table>

Histologic Slice

Red sirius | µIMAGER™
<table>
<thead>
<tr>
<th>Time from MI: 1-month</th>
<th>3-months</th>
<th>5-months</th>
<th>7-months</th>
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</thead>
<tbody>
<tr>
<td><strong>Short-axis</strong></td>
<td></td>
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<tr>
<td>basal</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
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<tr>
<td>median</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
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<tr>
<td>apical</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
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<tr>
<td><strong>Polar-maps</strong></td>
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<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td><img src="image15.png" alt="Image" /></td>
<td><img src="image16.png" alt="Image" /></td>
</tr>
</tbody>
</table>
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

Groupe Cell Therapy (n = 7)

MNC harvest (100 ml) (UTCT)

Selection - Cell preparation

Surgical procedure of CABG

3H

Infarct area

Intramycardial injection (20-40 injections; dans la zone infarcie)
CARDIAC CELL THERAPY IN PERFUSION STATUS

Maureira, Tran & Marie., *JNM.*, in press 2012
Patient good responder = Existence of a residual ischemia!
Patient non responder = NO residual ischemia!
LIFE IN THE SCHOOL OF SURGERY