



UNIVERSITÉ DE NANTES



École Nationale Vétérinaire, Agroalimentaire et de l'Alimentation Nantes Atlantique
Santé et alimentation au cœur de la vie



l'institut du thorax

Impact of the human adult muscle-derived stem cells “MuStem cells” in the context of myocardial infarction

Alice RANNOU, *Ph.D. Student*
PAnTher INRA/Oniris UMR 0703
Nantes, France

December, 13th 2018

INRA-Oniris UMR703 PAnTher
Physiopathologie Animale et bioThérapies du muscle et du système nerveux



Scientific context

Myocardial infarct (MI)

Leading cause of mortality and morbidity worldwide

- ✓ France: 120,000 cases a year (12,000 of death)
- ✓ US: 1.5 million cases a year (450,000 of death)

Inserm, Société française de cardiologie, www.american-hospital.org

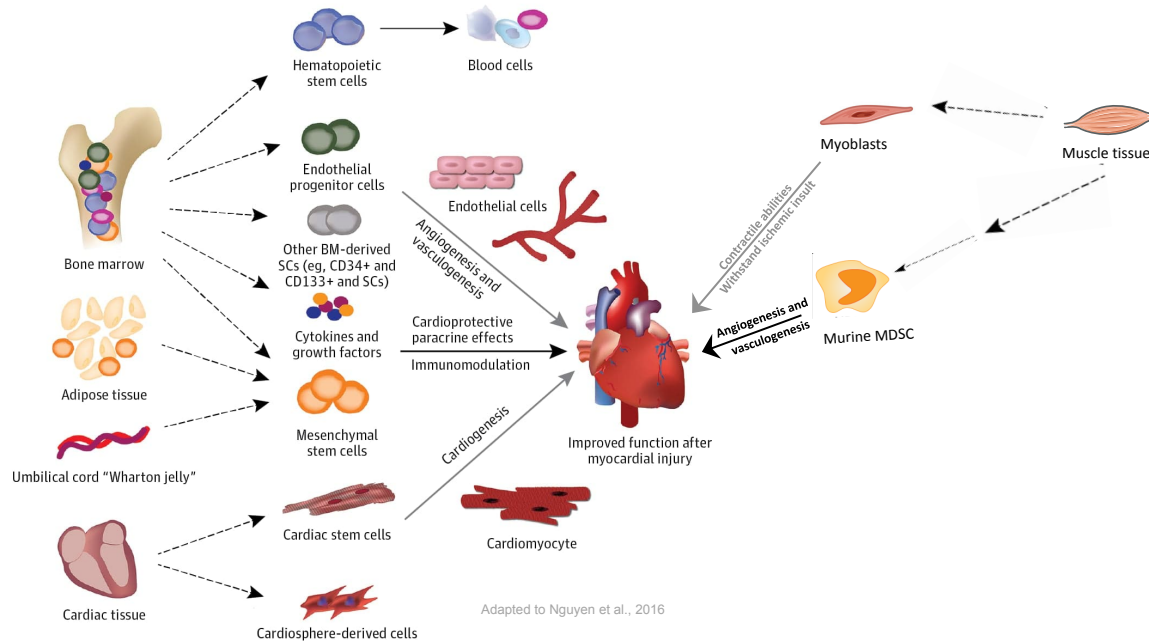
Treatment: reperfusion or transplantation

- ✓ More or less efficient
- ✓ Many complications: rhythm disorder, chronic heart failure...

→ Incomplete care

Need to find **therapeutic solutions** to **improve the tissue remodelling**

Cell therapy



Conclusion:

- Any or short-term effects
- Effects independent of cell presence
- Deleterious side effects
- Lack of reproducibility

Scientific context

Myocardial infarct (MI)

Leading cause of mortality and morbidity worldwide

- ✓ France: 120,000 cases a year (12,000 of death)
- ✓ US: 1.5 million cases a year (450,000 of death)

Inserm, Société française de cardiologie, www.american-hospital.org

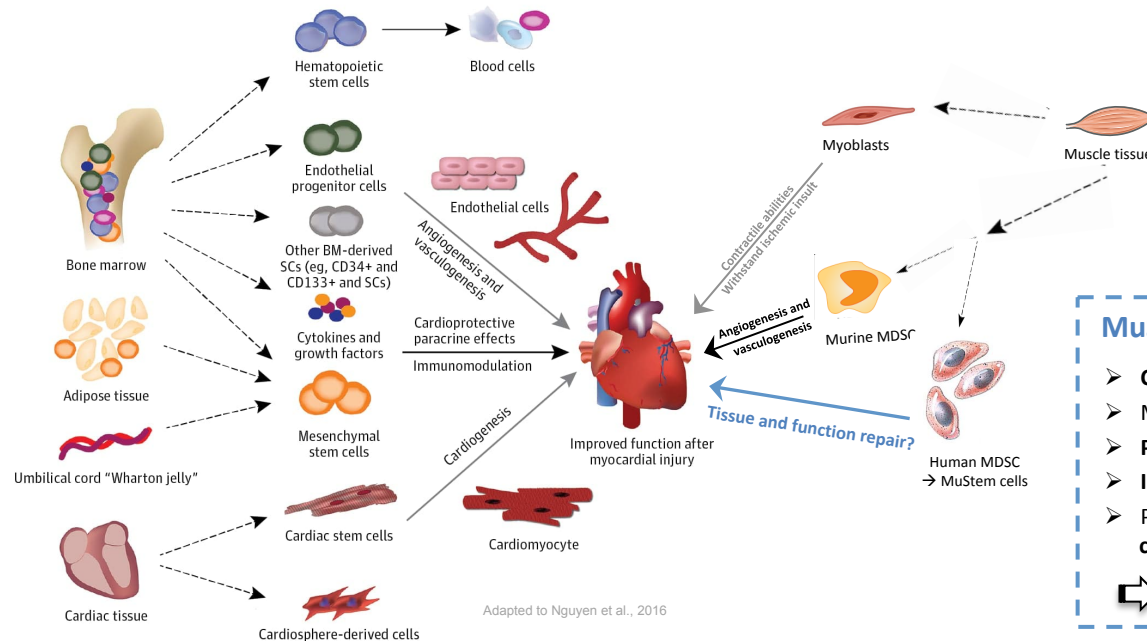
Treatment: reperfusion or transplantation

- ✓ More or less efficient
- ✓ Many complications: rhythm disorder, chronic heart failure...

→ Incomplete care

Need to find **therapeutic solutions to improve the tissue remodelling**

Cell therapy



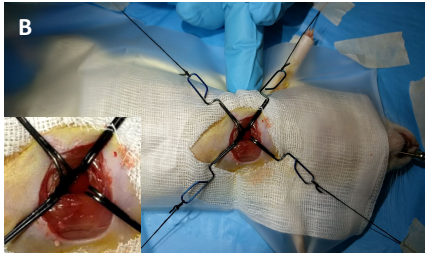
MuStem cells (Rouger *et al.*, 2011; Robriquet *et al.*, 2015,2016; Lardenois *et al.*, 2016; Lorant *et al.*, 2018; Saury *et al.*, 2018)

- Cell survival and migration ability *in vivo*
- Muscle regeneration
- Paracrine effects & Global tissue remodeling in dystrophic context
- Immunomodulatory properties
- Primitive cells (oligopotency, complex phenotyping including cardiac markers)

➡ Promising biological tool for regenerative medicine

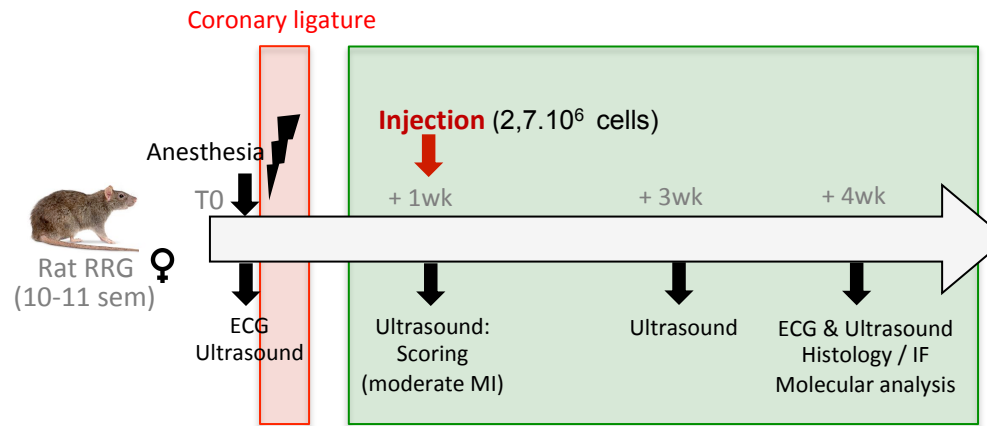
Design of the study

➤ Set up of the surgery



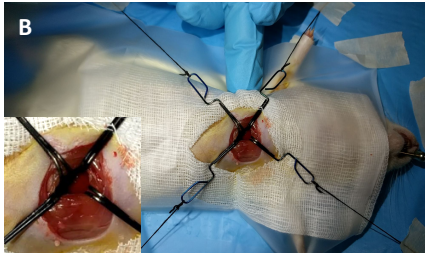
Cohort:
n=10 NaCl-injected rats
n=11 Cell-injected rats

Set-up and validation of the experimental protocol



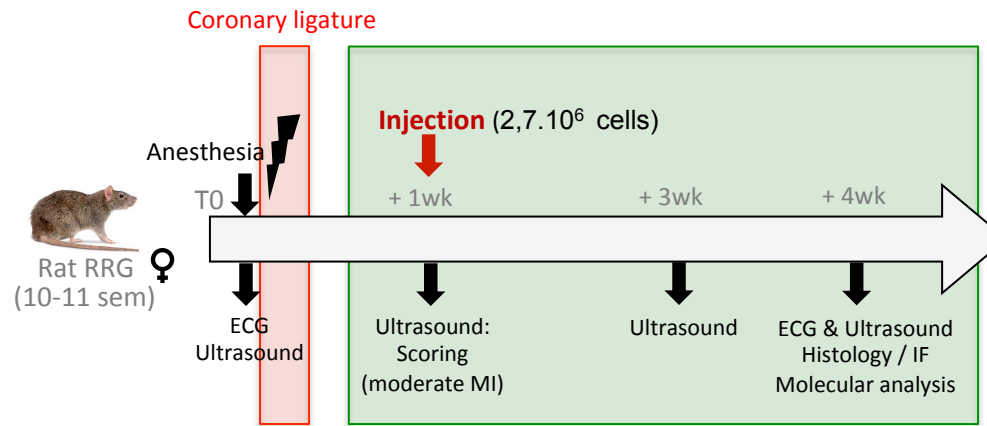
Design of the study

➤ Set up of the surgery

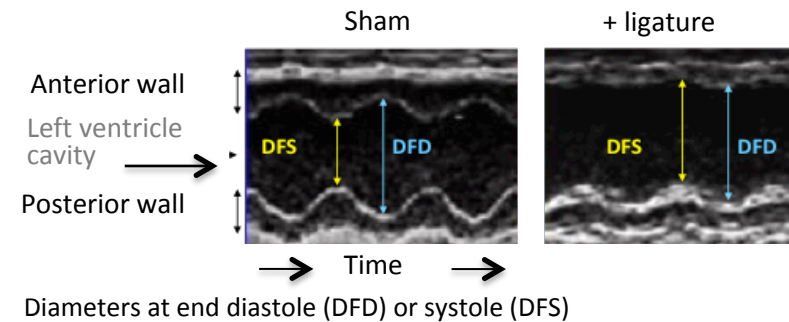
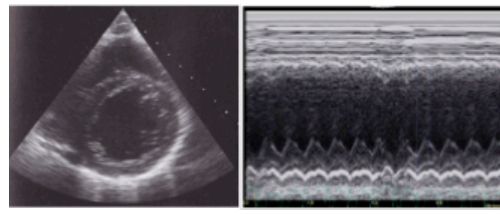
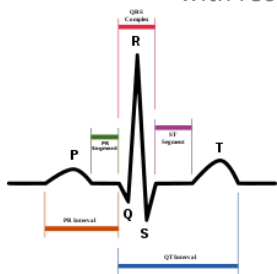


Cohort:
n=10 NaCl-injected rats
n=11 Cell-injected rats

Set-up and validation of the experimental protocol

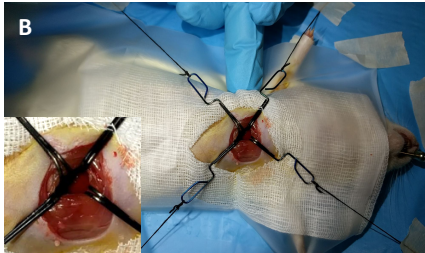


➤ ECG and ultrasound: Plane of incidence « small axis » combined with recording in « time-movement » mode



Design of the study

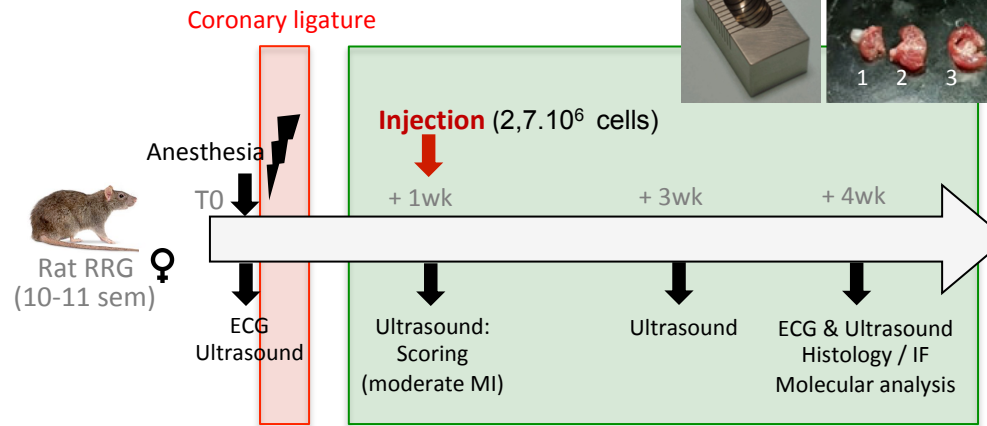
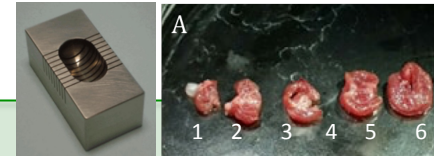
➤ Set up of the surgery



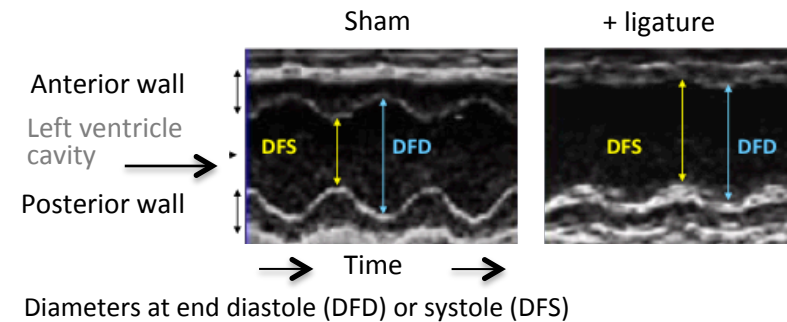
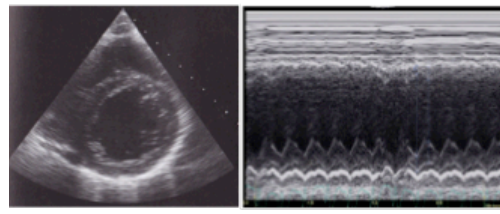
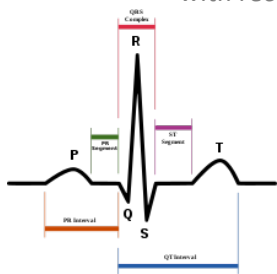
Cohort:
n=10 NaCl-injected rats
n=11 Cell-injected rats

Set-up and validation of the experimental protocol

➤ Rat heart slicer matrix



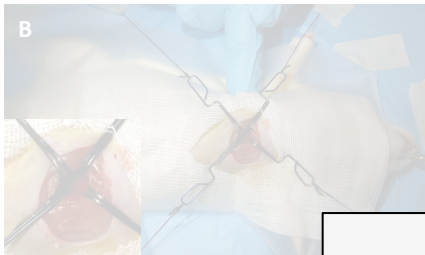
➤ ECG and ultrasound: Plane of incidence « small axis » combined with recording in « time-movement » mode



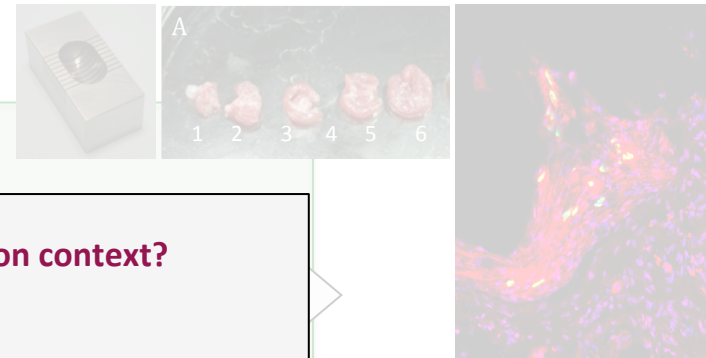
Design of the study

Set-up and validation of the experimental protocol

➤ Set up of the surgery



➤ Rat heart slicer matrix



Coronary ligature

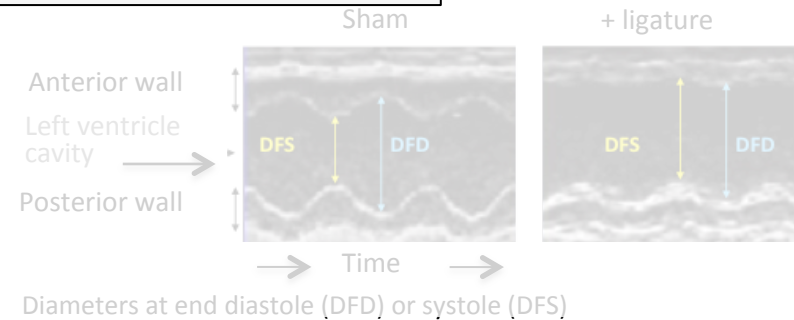
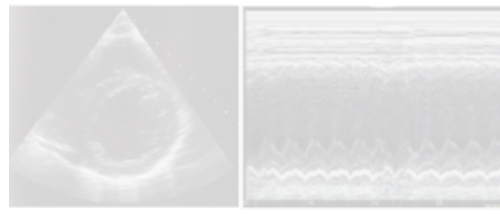
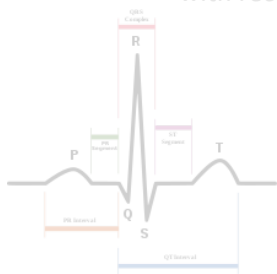
Injection ($2,7 \cdot 10^6$ Cells)

Could MuStem cells be useful in heart lesion context?

✓ Engraftment of MuStem cells ?

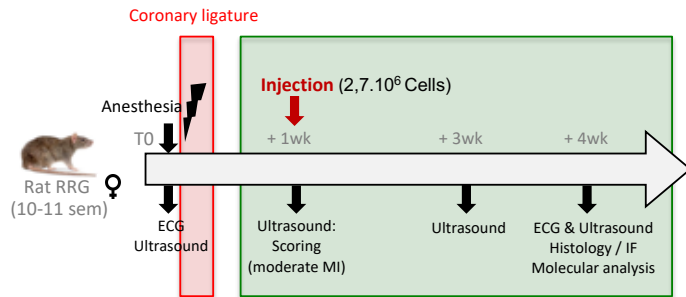
Cohort :
n=10 NaCl injected
n=11 Cells injected

➤ ECG and ultrasound: Pl...
with recording

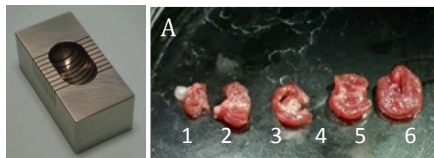


Engraftment of MuStem cells in myocardial infarction context

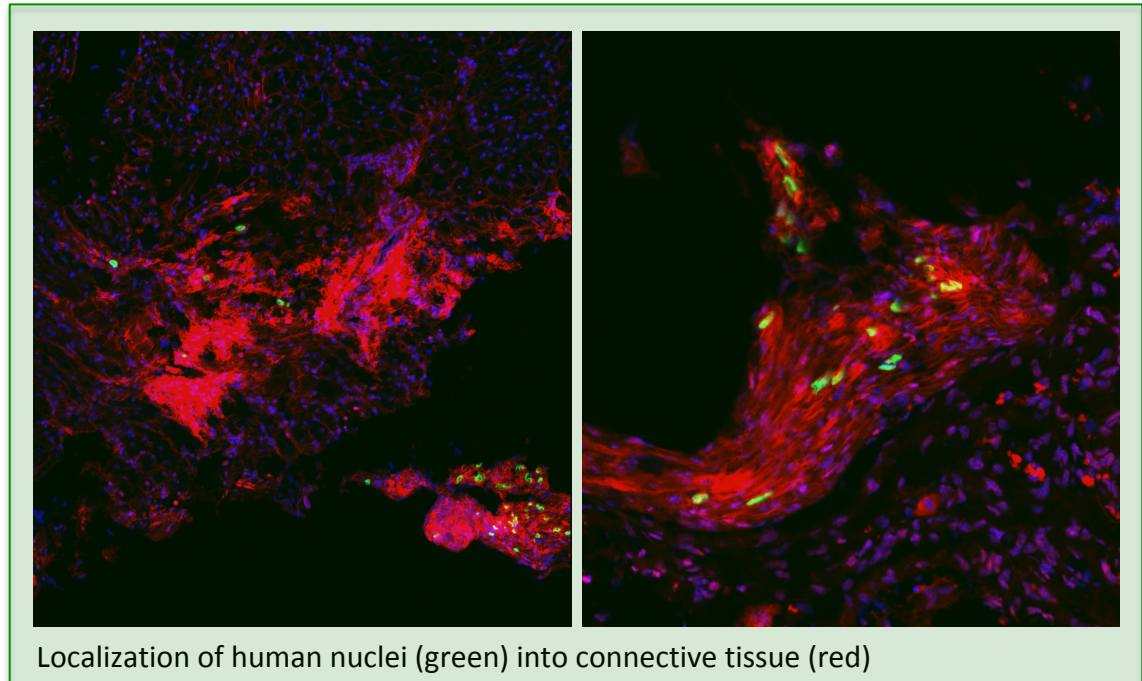
Preliminary results:



➤ Rat heart slicer matrix



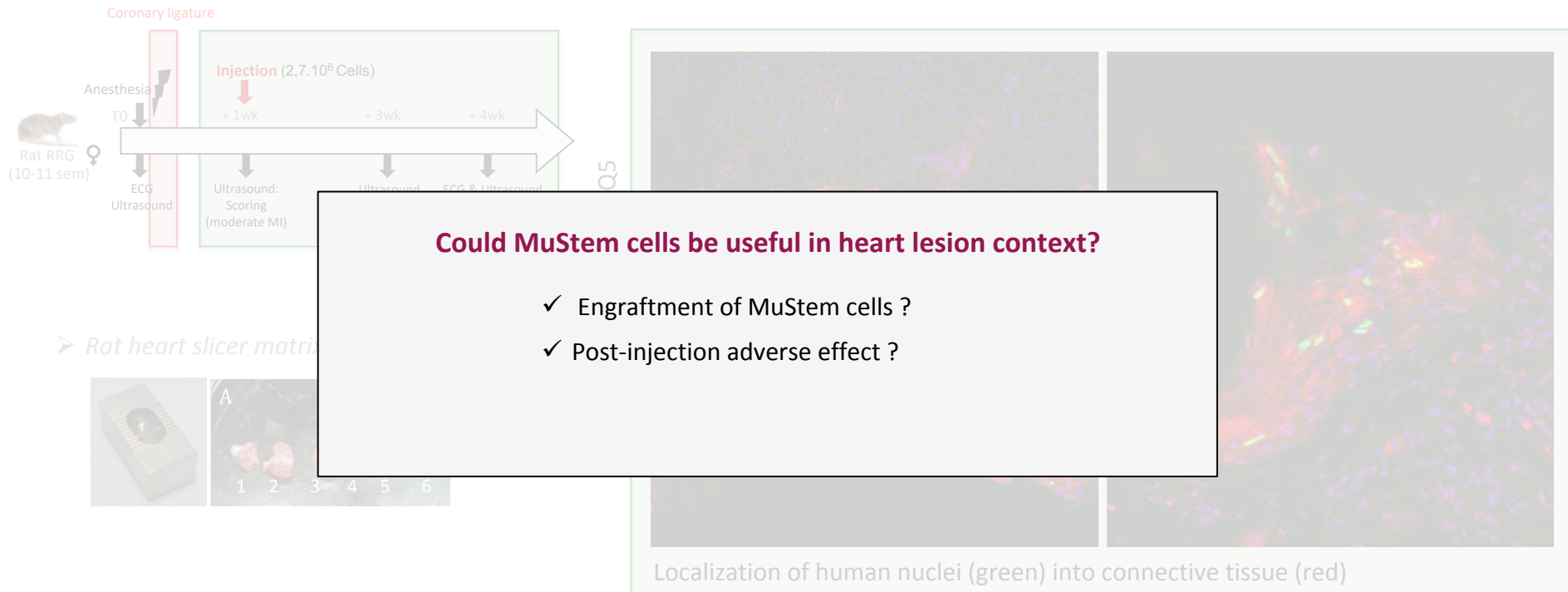
hLamin A/C / WGA / DRAQ5



Capacity to fit into the host tissue and always present 21 days post-injection

Engraftment of MuStem cells in myocardial infarction context

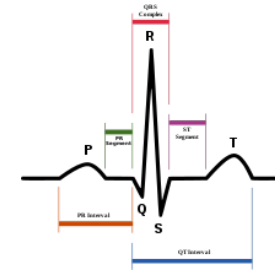
Preliminary results:



Capacity to fit into the host tissue and always present 21 days post-injection

MuStem cell implantation can lead to side effects ?

ECG analysis:



Preservation of the ECG pattern at d28

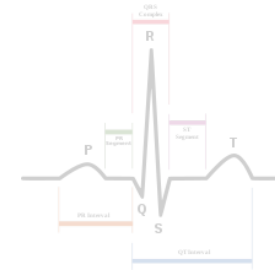
- Same cardiac frequency
- Unchanged duration for: P-wave, QRS complex and QT interval



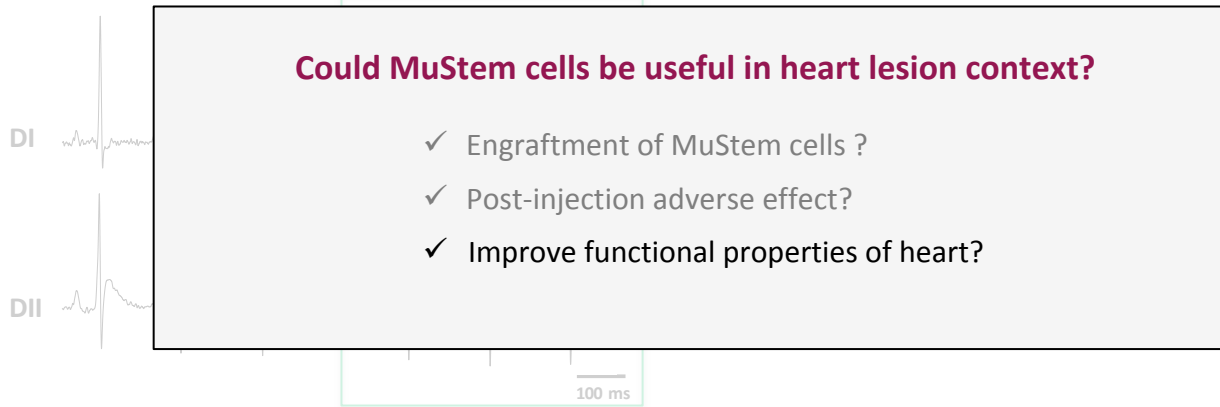
No arrhythmia subsequently to human cell implantation

MuStem cells implantation can led to side effects ?

ECG analysis:



Cells injected rats
Before infarction 28 days post-infarction



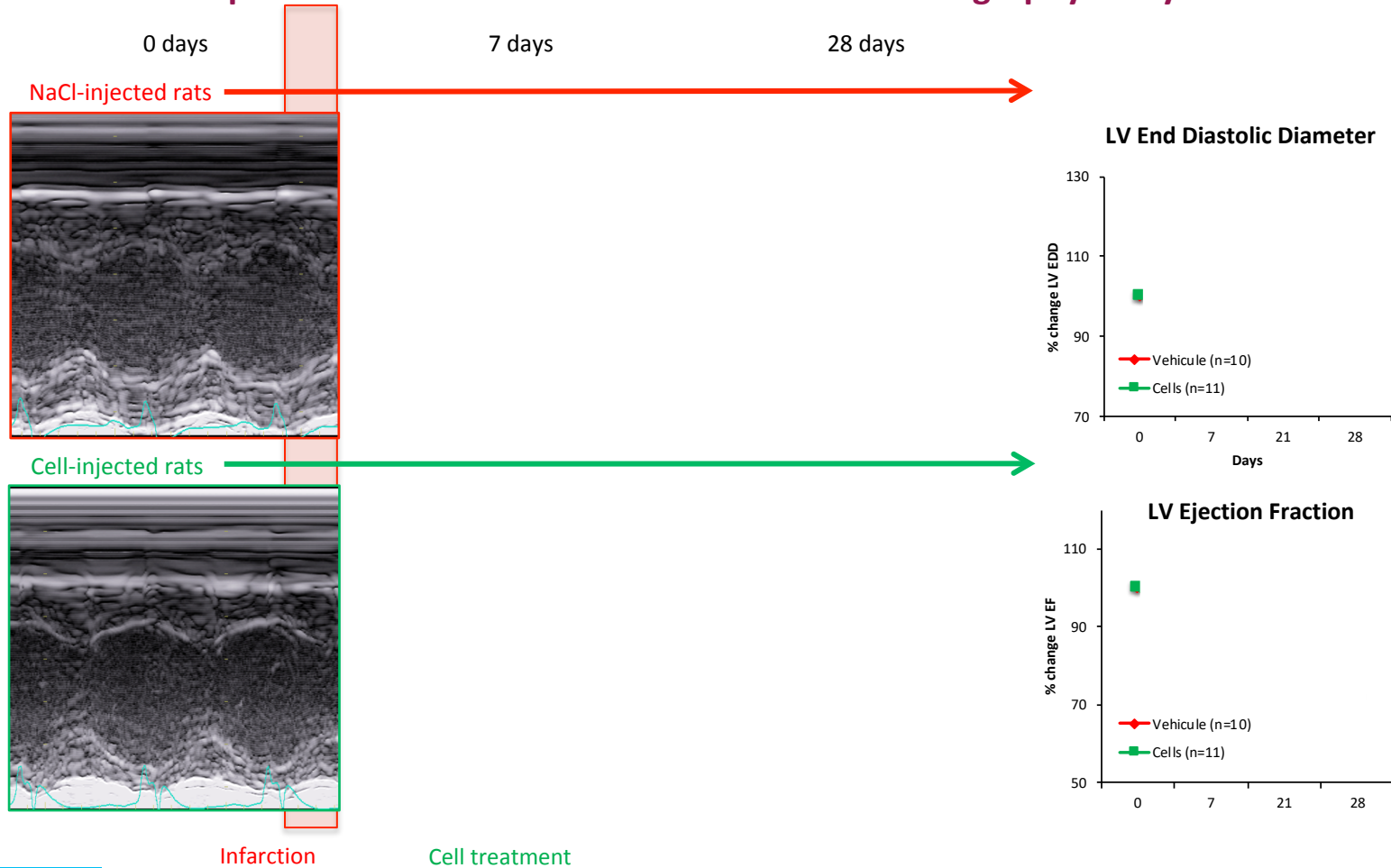
ern at d28

r: P-wave, QRS complex

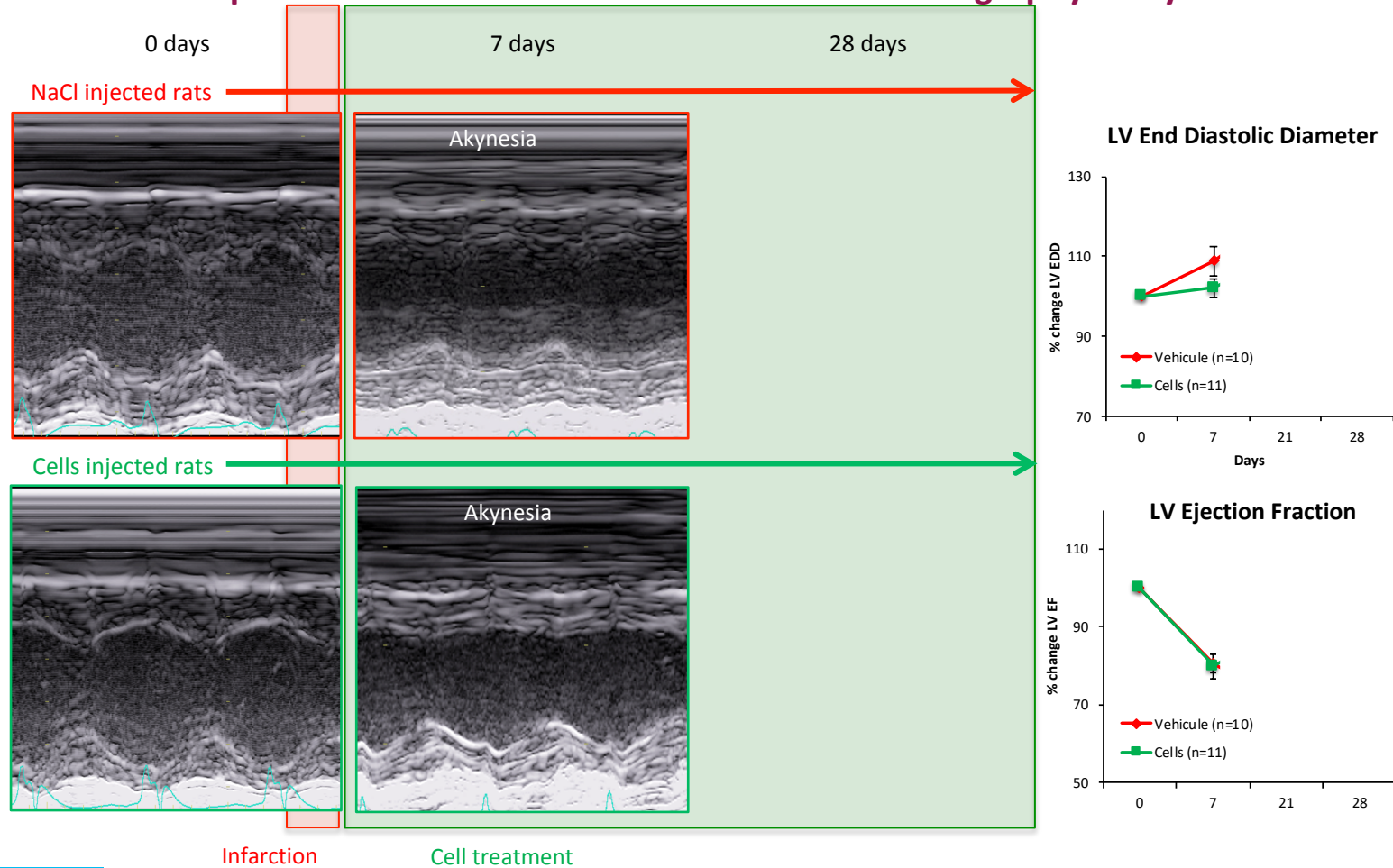


No arrhythmia subsequently to human cell implantation

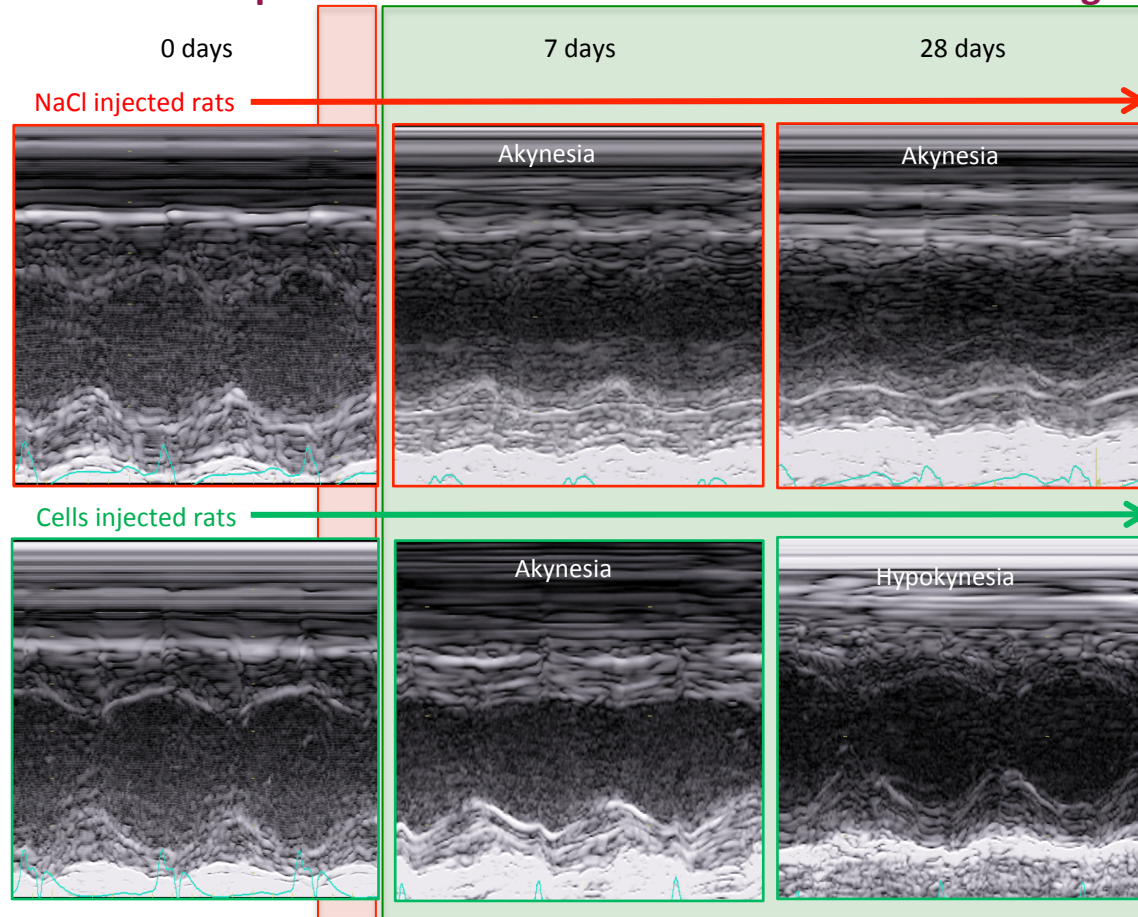
Impact of MuStem cells on cardiac function: Echography analysis



Impact of MuStem cells on cardiac function: Echography analysis



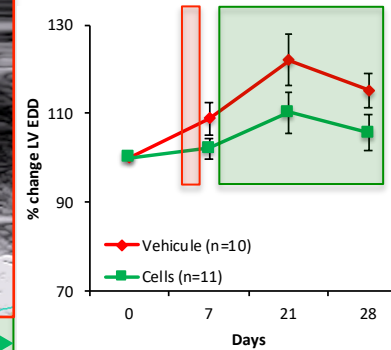
Impact of MuStem cells on cardiac function: Echography analysis



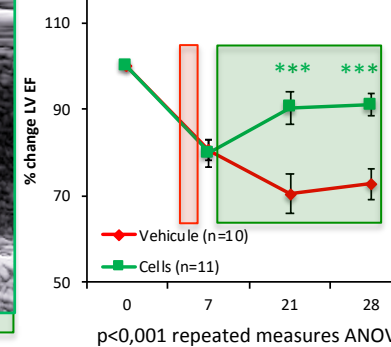
Infarction

Cell treatment

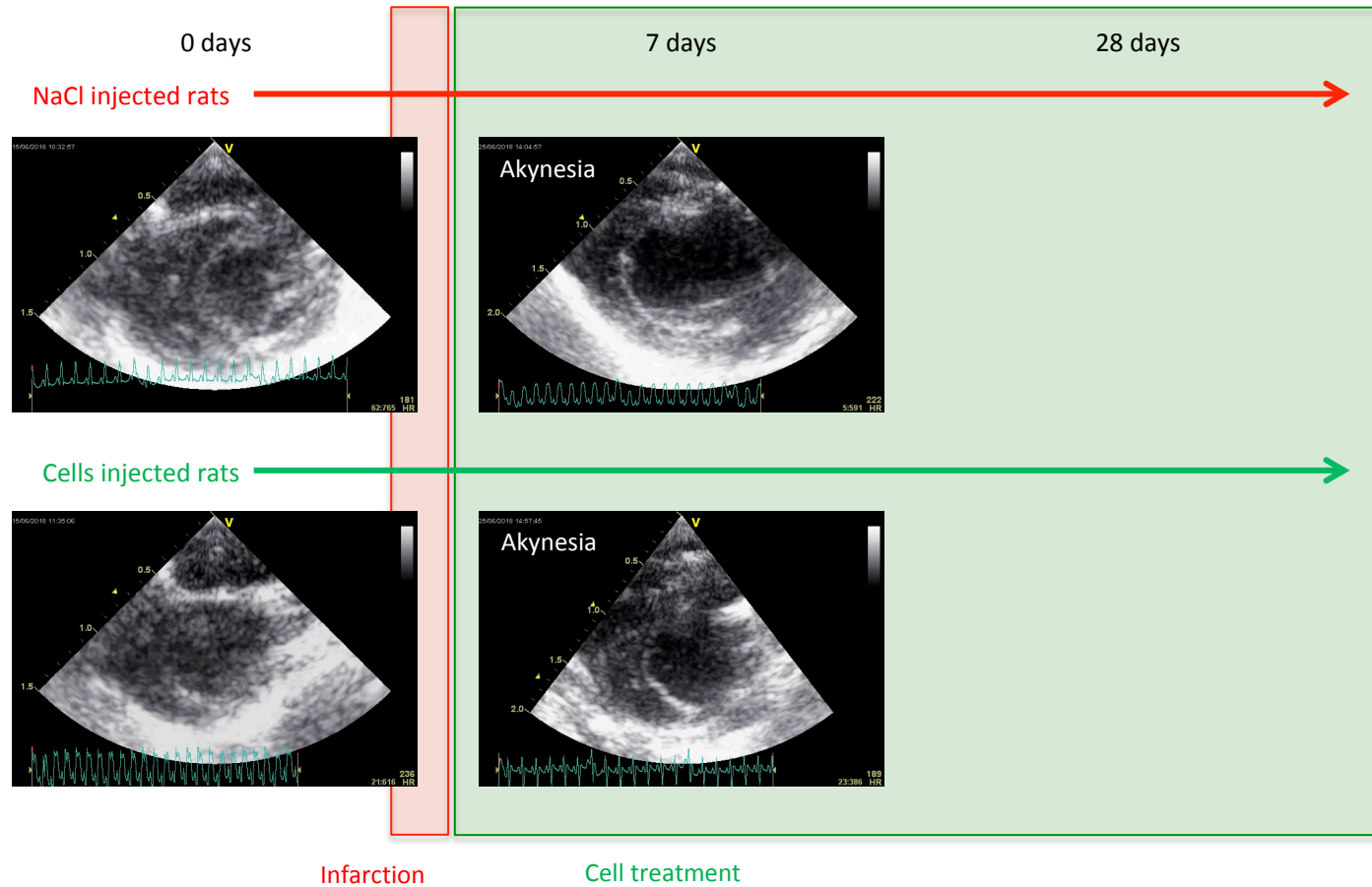
LV End Diastolic Diameter



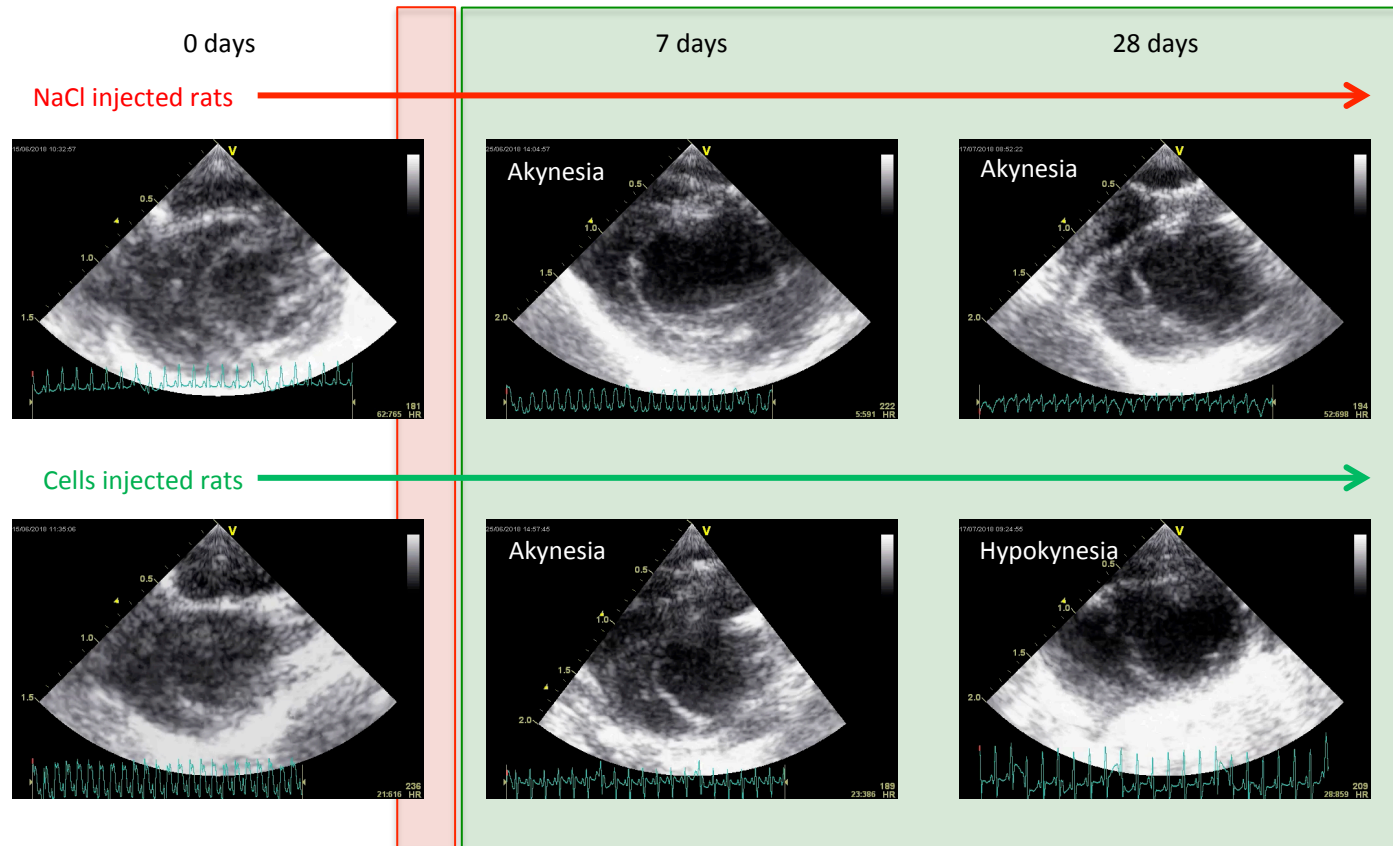
LV Ejection Fraction



Impact of MuStem cells on cardiac function: Echography analysis

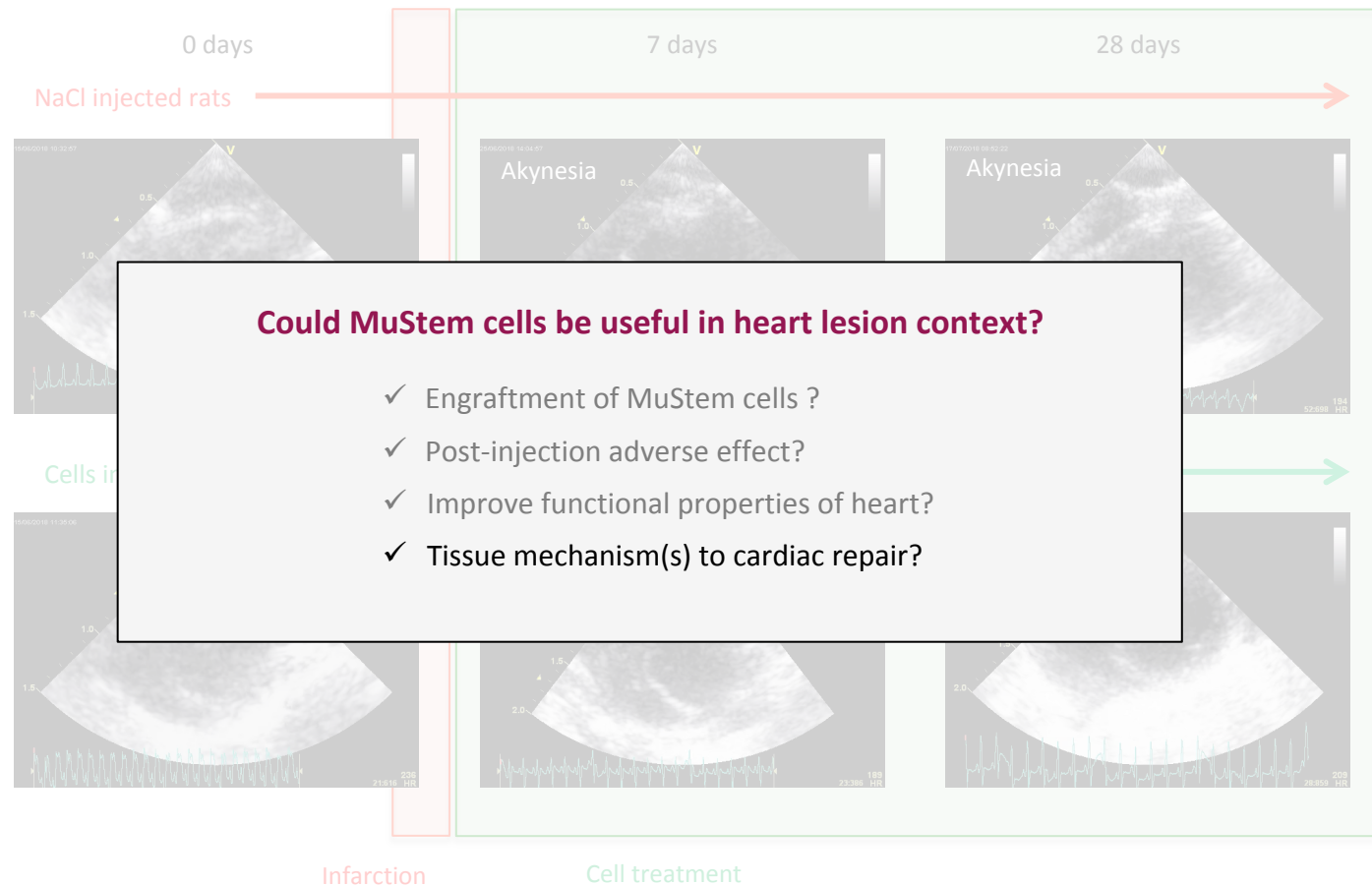


Impact of MuStem cells on cardiac function: Echography analysis



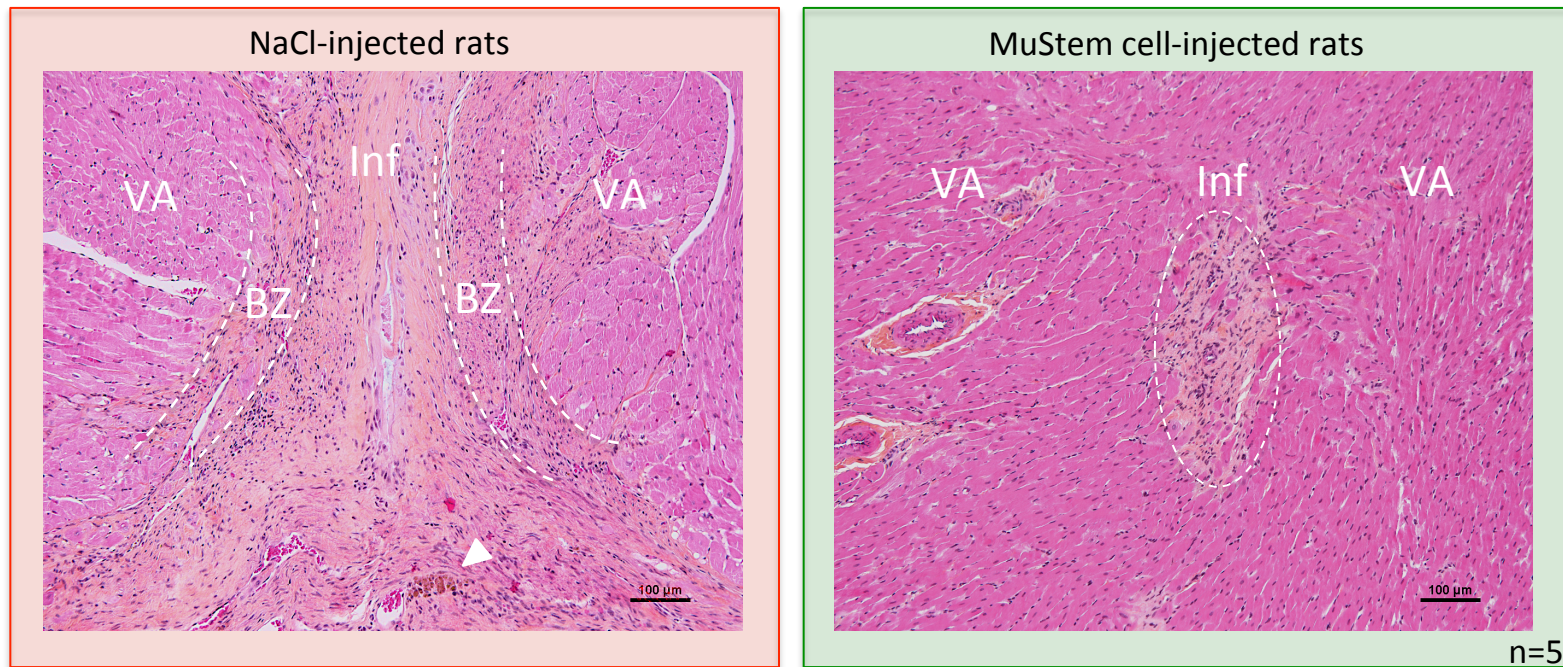
Capacity to modulate the functional & structural features of infarcted heart

Impact of MuStem cells on cardiac function: Echography analysis



MuStem cell effects on tissue remodelling

28 days



- Large fibrotic tissue
- 3 different area :
 - Viable area (VA)
 - Border zone (BZ)
 - Infarct (Inf)

- Small to moderate fibrotic tissue
- Localized area



MuStem cells seem to limit the extension of the fibrotic process

Take home messages and burning questions

Conclusion

MuStem cells

- **Engraft and maintain** in infarcted myocardium
- Partially restore **contractility**
- **Limit infarct size**

Work in progress

- ✓ Determine **the engraftment rate**
- ✓ Learn about **phenotype** they acquire *in situ*
 - How do MuStem cells behave: skeletal, cardiac or hybrid fibers?
 - Are MuStem cells cycling?
- ✓ Learn about **pericardic sphere remodelling**
 - Fibrotic tissue (quantitative data)
 - Neovascularisation

Acknowledgements



➤ UMR 703 INRA/Oniris

Karl Rouger
Laëtitia Guevel
Isabelle Leroux
Marine Charrier
Candice Babarit
Larcher Thibaut
Mireille Ledevin
And all the UMR703 PAnTher team



➤ Institut du thorax

Flavien Charpentier
Jean Mérot
Guillaume Lamirault
Gilles Toumaniantz
Agnès Hivonnait

➤ Financial support



RESEARCH
EDUCATION
INNOVATION) in Pays
de la Loire

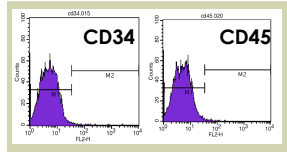


CE PROJET EST COFINANCÉ PAR
LE FONDS EUROPÉEN DE DÉVELOPPEMENT RÉGIONAL

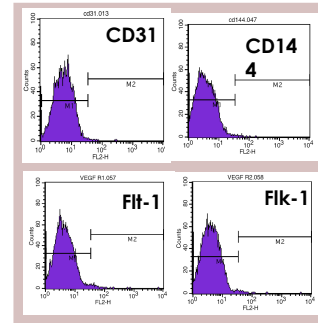
FEDER-FLS 2014-2020
(n° PL0003686)

Les cellules hMuStem (suppléments)

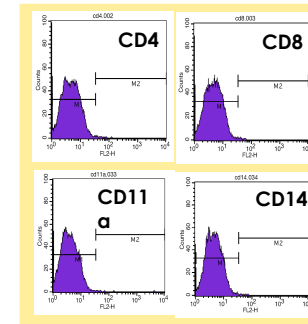
Hematopoietic markers



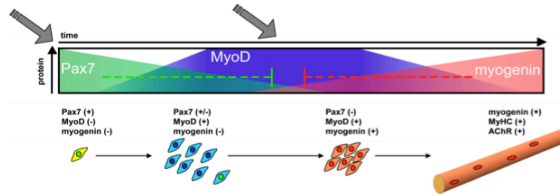
Endothelial markers



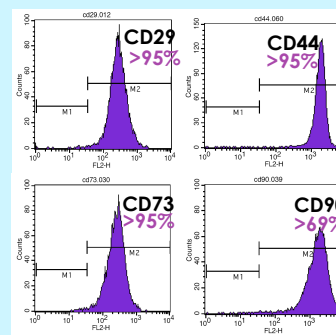
Blood markers



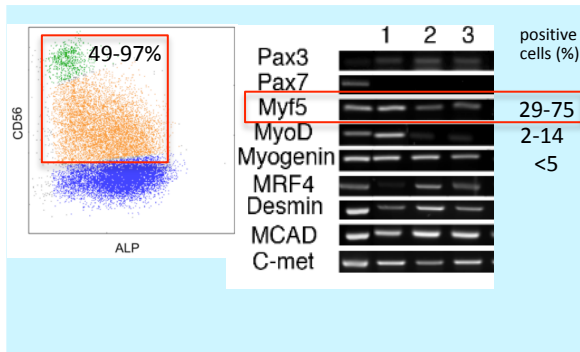
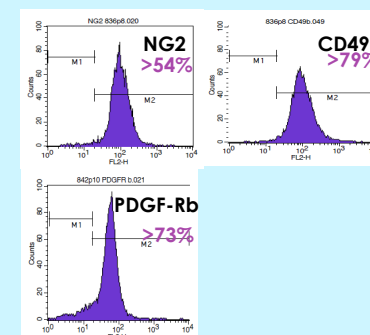
Myogenic markers



Mesenchymal markers

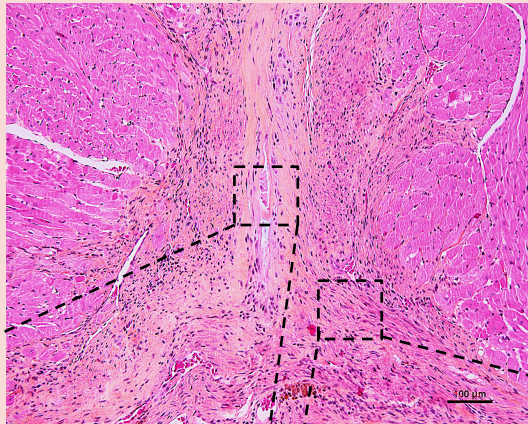


Perivascular markers



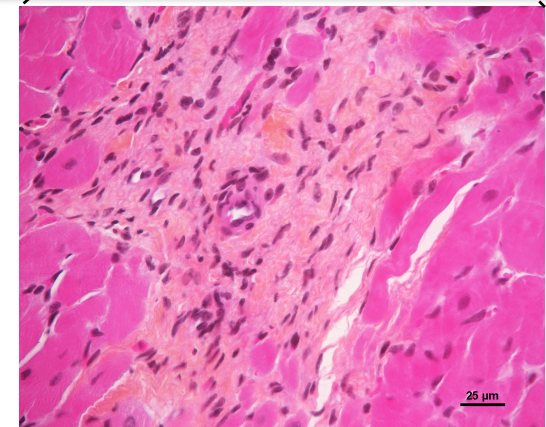
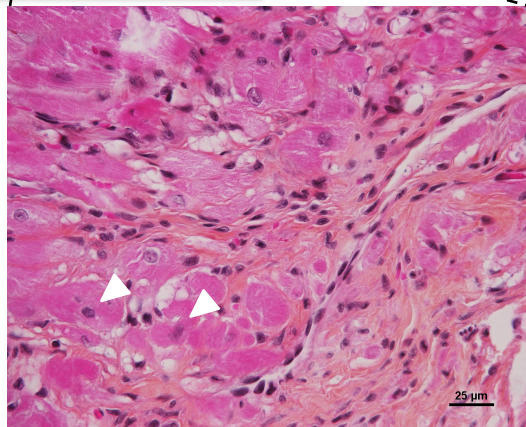
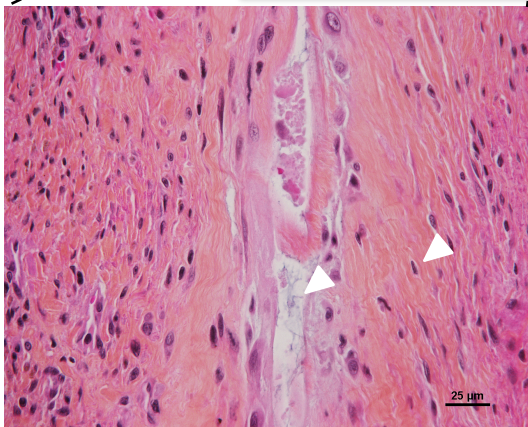
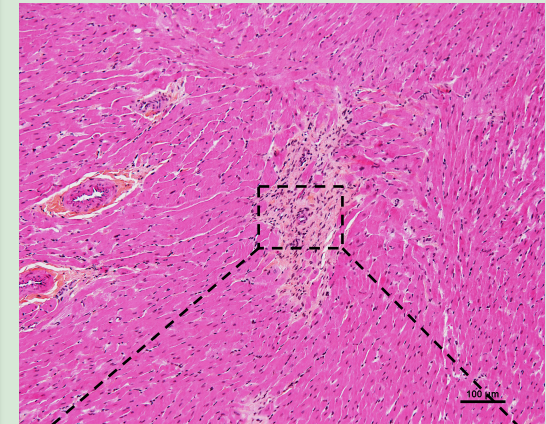
MuStem cells effects on tissue remodelling

NaCl Injected rats



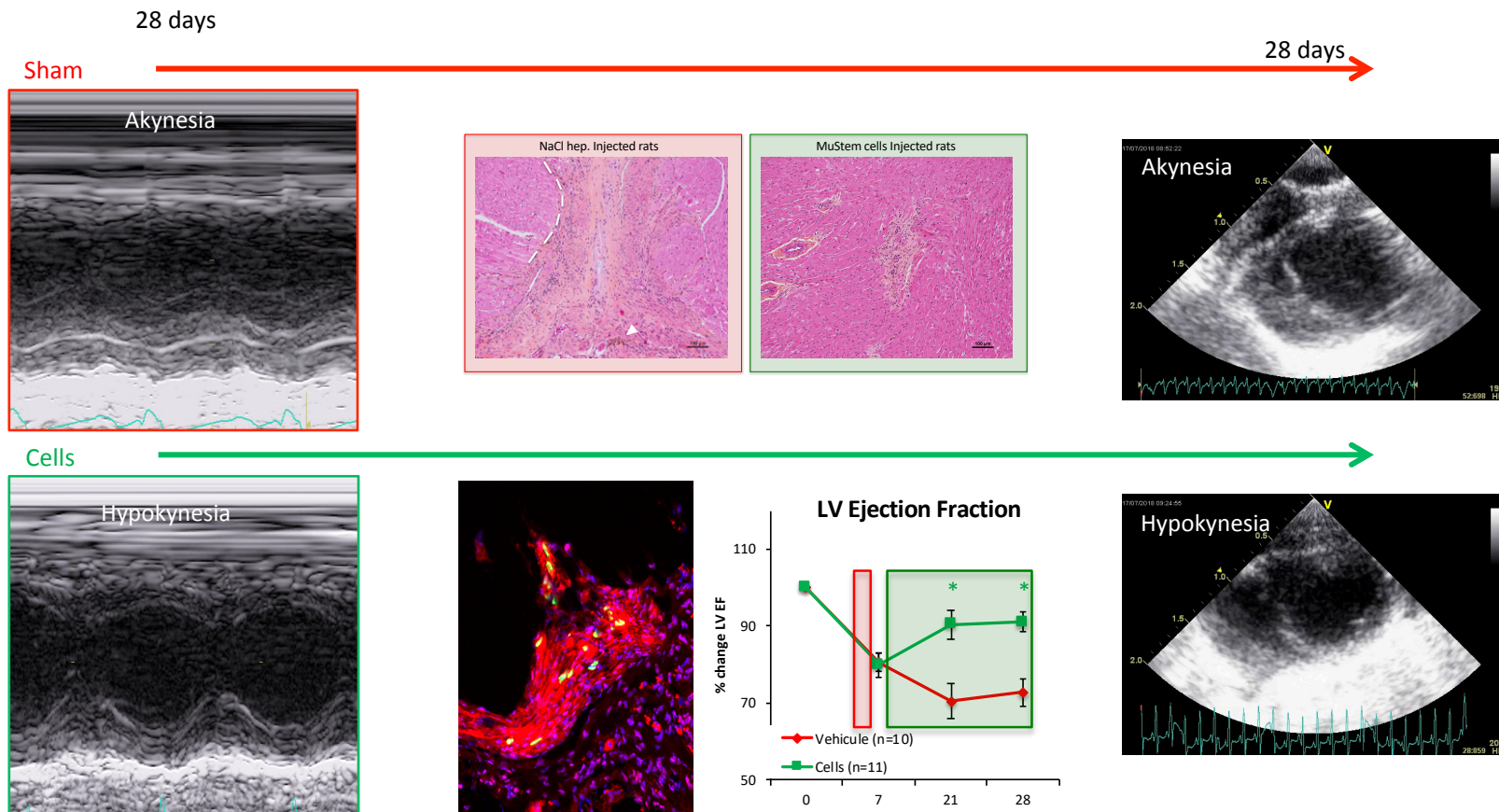
- Presence of activated fibroblasts
- Calcium crystals in necrotic area
- Ground substance
- Picnotic cardiomyocyte nuclei

MuStem cells Injected rats



MuStem cells seem to limit the fibrotic process

Could MuStem cells be useful in heart lesion context?



MuStem cells effects on tissue remodelling: fibrotic area

Hes et picrosirius

