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Repair of myocardial infarction with human adult muscle-derived stem cells “MuStem”

Alice Rannou, Gilles Toumaniantz, Thibaut Larcher, Isabelle Leroux, Mireille Ledevin, A Hivonnait, S. Menoret, Ignacio Anegon, F. Charpentier, Karl Rouger, et al.

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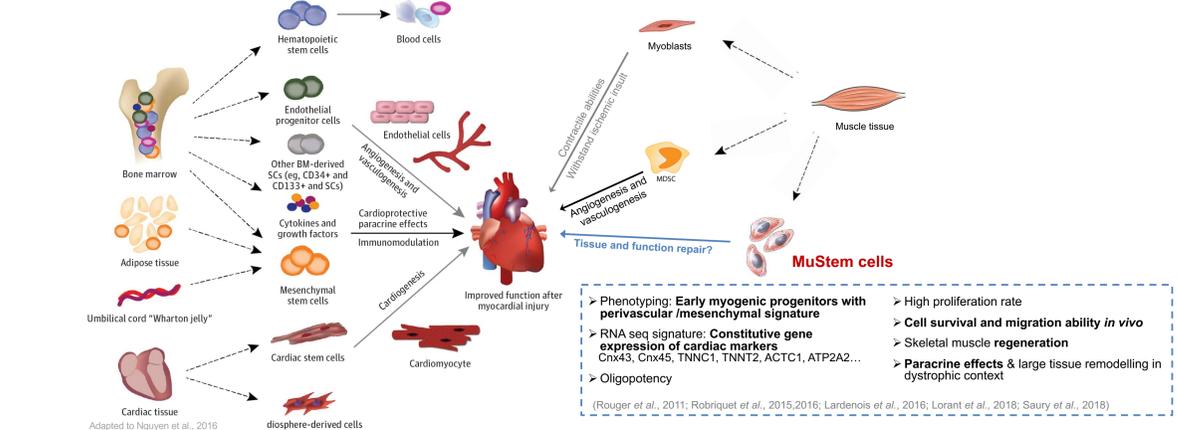
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Rannou A ^{1,2,3,#}, Toumaniantz G ^{2,3}, Larcher T ¹, Leroux I ¹, Ledevin M ¹, Hivonnait A ², Menoret S ⁴, Aneon I ⁴, Charpentier F ², Rouger K ^{1*}, Guével L ^{1,3*}

1 Panther INRA/Oniris UMR 703, Oniris, Nantes, France
2 INSERM UMR 1087/CNRS UMR 6291, Institut du Thorax, Nantes, France
3 University of Nantes, Nantes, France
4 INSERM UMR 1064/facility TRIP/UMRS3556, Center for Research in Transplantation and Immunology, Nantes, France
* Equal contribution
alice.rannou@univ-nantes.fr

Introduction

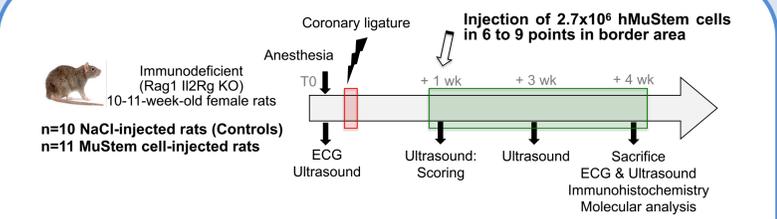
Myocardial infarction is a leading cause of morbidity and mortality worldwide. Although medical and surgical treatments can significantly improve patient outcomes, no **treatment is currently available** to generate new contractile tissue or reverse ischemic myocardium. Driven by the recent understanding that repair mechanism could be made in the injured myocardium, the **use of stem cells has emerged as a promising therapeutic approach** with high expectations. The literature describes the use of cells from various sources with demonstration of tissue and/or functional benefits in both animal models and Human; however, more studies are needed to directly compare cells of various origins in efforts to draw conclusions on the most appropriate source in order to positively impact on the heart tissue and function remodelling. Over the past ten years, we isolated a **marginal adult stem cell population**, we called **MuStem cells**, from dog and human successively and assigned to them a **robust myogenic regenerative potential** into dystrophic or injured muscle context. A panel of interesting features described below was also added to their characterization.



The **main objective** of the present study is to determine whether the human MuStem cell agent can act positively in this acute context of heart disease following its local administration.

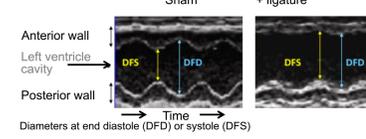
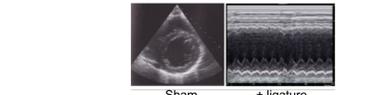
List of opening questions: Can MuStem cells rescue cardiac function? Can they impact on tissue remodelling? Do they engraft in cardiac tissue?

Materials & Methods



➤ **Ultrasound:** to score the infarct and to follow the course of the phenotype in terms of function and structural remodelling.

The percentage of ejection fraction is obtained with the plane of incidence « small axis » combined with recording in « time-movement » mode. The left ventricle and diastolic diameter is analysed to highlight a potential ventricular dilatation.



➤ **ECG:** to explore cardiac arrhythmias 6 derivations are realized

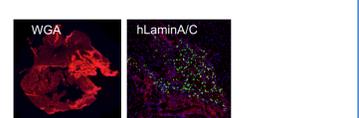
Parameters obtained:
✓ Cardiac frequency
✓ Duration of P-wave, QRS complex & QT interval

➤ **Rat heart slicer matrix**



Each heart has been cut off in slices frozen or put in paraffin to allow full histological investigations.

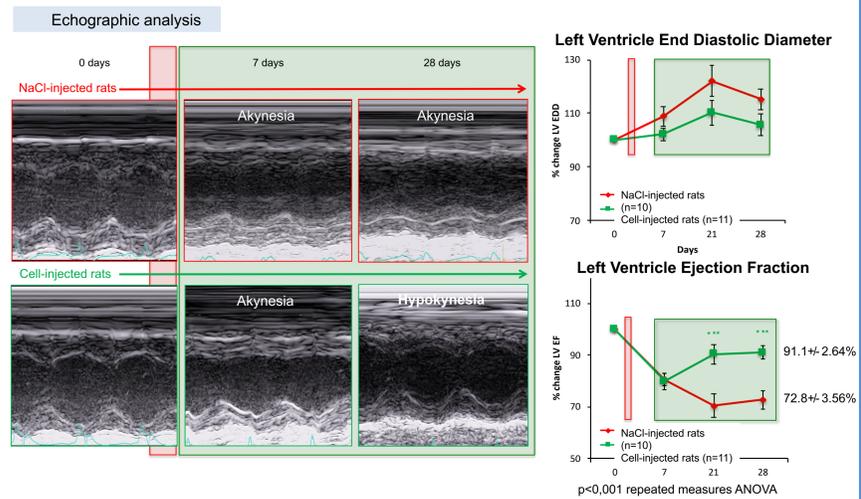
➤ **Histology**



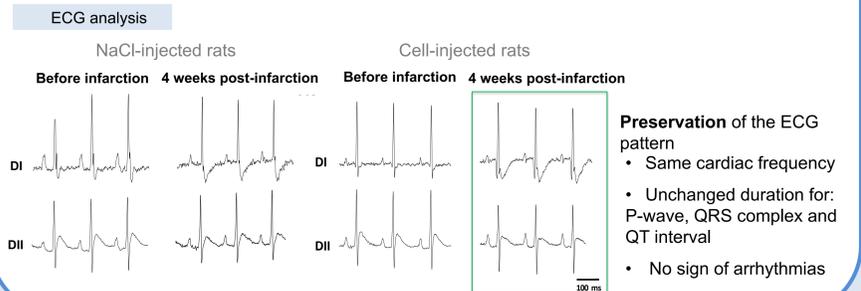
WGA (Wheat germ agglutinin) is a lectin used to highlight extracellular matrix.
hLamin A/C protein is used to label human cells into rat tissue.

Results – Part I

Functional and structural benefits consequently to hMuStem cell injection without demonstration of rhythm disturbances

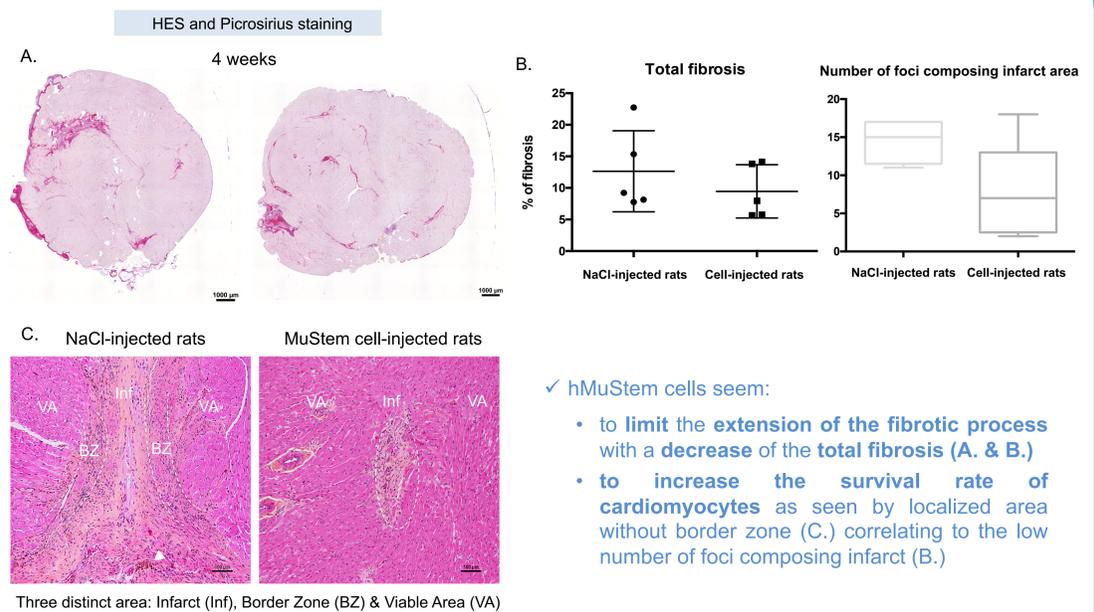


✓ hMuStem cells **partially restore** the heart function that results in **hypokinesia** in treated rats and to an improvement of the LVEF 3 weeks post-injection.



Results – Part II

Large tissue remodelling induced following hMuStem cell injection

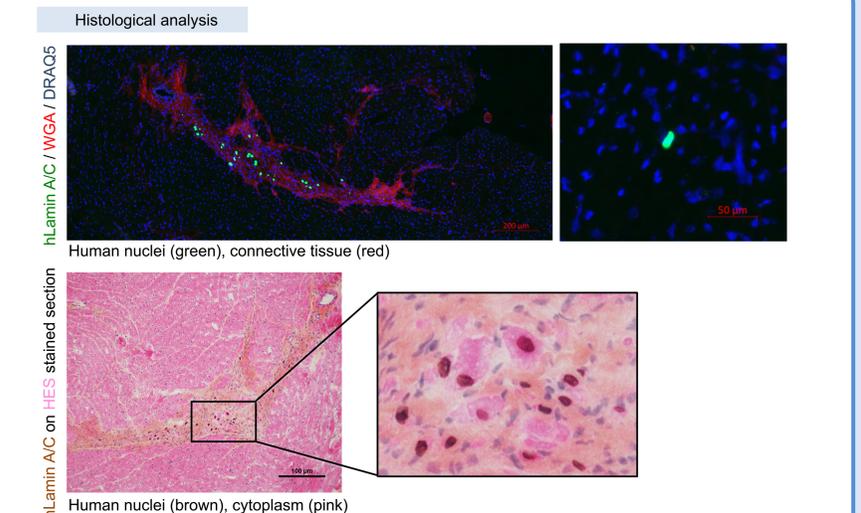


✓ hMuStem cells seem:

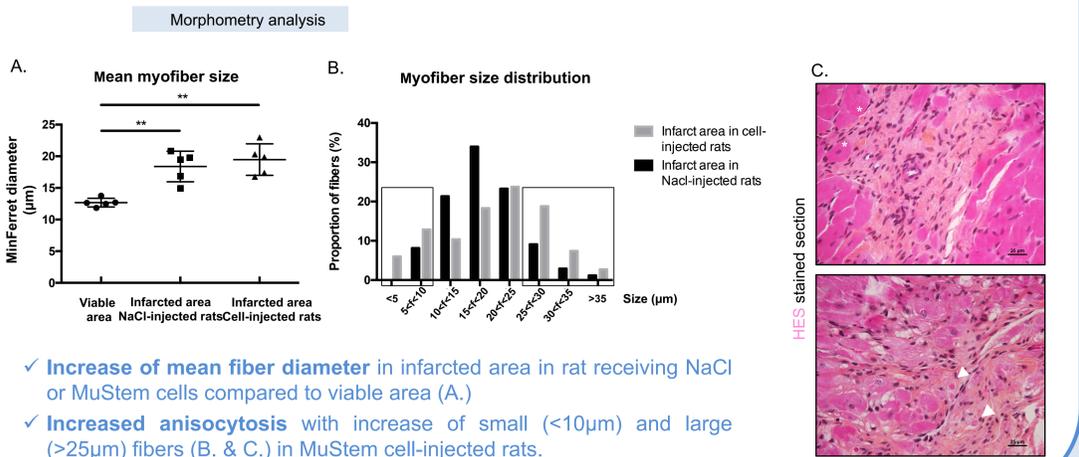
- to limit the extension of the fibrotic process with a decrease of the total fibrosis (A. & B.)
- to increase the survival rate of cardiomyocytes as seen by localized area without border zone (C.) correlating to the low number of foci composing infarct (B.)

Results – Part III

Engraftment of hMuStem cells in myocardial infarction context



- Ability of the human MuStem cells to fit and to maintain into the host tissue 3 weeks post-injection.
- Predominant localization of human cells in connective tissue. However some are in cytoplasm of small cells.
- Presence of cells in the depth of the heart with at least 15 cells per slices.



- ✓ Increase of mean fiber diameter in infarcted area in rat receiving NaCl or MuStem cells compared to viable area (A.)
- ✓ Increased anisocytosis with increase of small (<10µm) and large (>25µm) fibers (B. & C.) in MuStem cell-injected rats.

Conclusion & Perspectives

Ability of hMuStem cells:

- To generate **functional and structural benefits** in the infarcted heart
- To limit the extension of the fibrotic process
- To **engraft and survive** into infarcted cardiac tissue 3 weeks post-injection

To confirm these results, the next steps will be:

- ✓ To provide quantitative data on the **engraftment rate** of MuStem cells
- ✓ To learn about the **phenotype** they acquire *in situ*:
 - Differentiation ?
 - Proliferative / quiescent state ?
 - Cell death ?
- ✓ To investigate the ability of MuStem cells to induce **angiogenesis**
- ✓ To determine the nature of small cells identified in remodelling tissue

Acknowledgements



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