Groups	CON (vehicle)		EVs		CDC	
	Baseline preinjection	10 weeks	Baseline preinjection	10 weeks	Baseline preinjection	10 weeks
LVEF (%)	27±3	29±7	27±4	29±13	28±5	32±8
EDVi (mL/m2)	93±17	98±19	81±11	97±29	84±9	89±20
ESVi (mL/m2)	68±13	71±19	59±9	71±31	60±8	62±21
Infarct Size (%)	25±7	12±3	21±5	10±2	21±3	10±3

Data presented as mean±standard deviation. LVEF: Left ventricular ejection fraction. EDVi: End diastolic volume indexed to body surface area. ESVi: End systolic volume indexed to body surface area. Infarct area is expressed as % of the left ventricle.

CMR-derived cardiac function parameters

Results: The epicardial administration was completed successfully in all cases. CMR-derived cardiac function parameters are shown in the table. No significant differences between groups were found in cardiac function at the end of the study, despite a trend towards improved function in CDC-treated animals compared to Control. VT inducibility was not significantly different between groups either. Masson's trichrome staining did not show pathological differences between groups in any of the studied zones: infarct core, infarct border or distal (healthy) tissue (Figure).
Conclusion: While the epicardial delivery of 30x106 CDC or their EVs is safe and technically easy 3 days after experimental MI in swine, it does not appear to have any beneficial effect on cardiac function. Our results do not support clinical translation of these therapies as implemented in this work.

Extracellular vesicles from mesenchymal stromal cells combined with tissue engineering for myocardial repair

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Introduction: Accumulating evidence supports the potential of extracellular vesicles (EVs) from mesenchymal stromal cells (MSC) as a therapy for cardiac healing after myocardial infarction (MI). Nevertheless, neither their efficient administration nor their therapeutic mechanisms are fully elucidated.
Purpose: To evaluate the preclinical efficacy of a tissue engineering approach to locally deliver porcine cardiac adipose tissue MSCs-derived EV (cATMSC-EV) in an acute MI pig model.
Methods: Pigs (n=24) were subjected to permanent ligation of the coronary artery. After 30 min, animals were randomized to Untreated or treated groups with a tissue engineered graft composed of a decellularized pericardial scaffold filled with peptide hydrogel and either cATMSC-EV purified by size exclusion chromatography (EV-treated group) or buffer (Control group) placed over the post-MI myocardium. Cardiac troponin levels and cardiac MRI revealed consistent myocardial damage and infarct size in all animals.
Results: After 30 days, cardiac function was significantly improved with less right ventricle (RV) dilation in the EV-treated group (RV ejection fraction 2 days post-MI vs 30 days: 44.5 ± 4.2 vs 40.6 ± 11.8 Untreated (p=0.836); 47.0 ± 8.0 vs 45.0 ± 5.9 Control (p=0.923) and 41.4 ± 10.0 vs 52.9 ± 7.0 EV-Treated (p=0.026)), indicating less myocardial remodelling and correlating with a decrease of fibrosis in the distal zone (0.61 ± 0.2 Untreated; 0.63 ± 0.25 Control vs 0.35 ± 0.20 EV-Treated; p = 0.03). MRI also showed a reduced scar size in EV-treated animals (3.7 ± 1.6 at 2d vs 2.9 ± 2.2 at 30d Untreated (p=0.795); 3.8 ± 2.2 vs 2.3 ± 0.7 Control (p=0.115) and 4.2 ± 3.1 vs 2.5 ± 1.7 EV-Treated (p=0.042)), concomitant with an increased vascular density in the infarct core (0.21 ± 0.13 Untreated; 0.25 ± 0.14 Control vs 0.41 ± 0.10 EV-Treated; p = 0.019), less macrophage infiltration (CD163+ cells/field: 13.9 ± 2.8 Untreated; 11.4 ± 3.0 Control vs 9.5 ± 1.5 EV-Treated; p = 0.026) and more with anti-inflammatory phenotype (%CD73+: 3.2 ± 0.7 Untreated; 2.6 ± 4.0 Control vs 18.7 ± 15.1 EV-Treated; p = 0.015). Surprisingly, local delivery of cATMSC-EV also triggered a systemic effect, reducing PBMC increase 2-days post-MI and modulating systemic CD73+ and CCR2+ monocytes, related to immunomodulation and fibrosis modulation.
Conclusions: These results highlight the clinical potential of cATMSC-EV in modulating key features of ischemic injury and promoting cardiac repair after MI.

	Group	2 days post-MI (mean ± SD)	30 days post-MI (mean ± SD)	*p* value
RVEF (ml)	Untreated	44.5 ± 4.2	40.6 ± 11.8	0.836
	Control	47.0 ± 8.0	45.0 ± 5.9	0.923
	EV-Treated	41.4 ± 10.0	52.9 ± 7.0	*0.026
Scar size (LGE mass; g)	Untreated	3.7 ± 1.6	2.9 ± 2.2	0.795
	Control	3.8 ± 2.2	2.3 ± 0.7	0.115
	EV-Treated	4.2 ± 3.1	2.5 ± 1.7	*0.042
Distal fibrosis (Collagen I area)	Untreated	n.a.	0.61 ± 0.20	
	Control	n.a.	0.63 ± 0.25	
	EV-Treated	n.a.	0.35 ± 0.20	*#0.03 vs Control*
Vascular density (Isolectin-B4+ area)	Untreated	n.a.	0.21 ± 0.13	
	Control	n.a.	0.25 ± 0.14	
	EV-Treated	n.a.	0.41 ± 0.10	†0.019
Macrophage infiltration (CD163+ cells/field)	Untreated	n.a.	13.9 ± 2.8	
	Control	n.a.	11.4 ± 3.0	
	EV-Treated	n.a.	9.5 ± 1.5	†0.026
Anti-inflammatory macrophages (%CD73+ of CD163+ cells/field)	Untreated	n.a.	3.2 ± 0.7	
	Control	n.a.	2.6 ± 4.0	
	EV-Treated	n.a.	18.7 ± 15.1	†0.015

*Abbreviations: RVEF: Right Ventricle Ejection Fraction; LGE mass: Low Gadolinium Enhanced mass; n.a.: not applicable. *p<0.05 by Paired One-way ANOVA. #p<0.05 by T-student test. †p<0.05 by One-way ANOVA with Tukey post-hoc analysis.*

Summary of most relevant results

Basic Science–Biomarkers

LGALS-3 containing haplotype block tag variants in association with cardiac parameters changes within six months after the first acute myocardial infarction

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After myocardial infarction (MI) and consequential ischemia, the heart undergoes a set of geometric and functional changes. In the early days after injury, these changes, defined as cardiac remodeling, are the powerful factor that preserves cardiac function and promotes survival. However, it may continue for months after MI and eventually lead to adverse remodeling with impaired systolic function and reduced myocardial contractility and further cardiovascular complications, such as heart failure (HF). Left ventricular (LV) ejection fraction (EF) is widely used as an index of systolic function in cardiac patients. However, global myocardial strain has been found to be superior to the conventional parameters, such as LVEF, in terms of assessment of cardiac performance after MI. Galectin-3 (gal-3) is a multifunctional protein involved in a variety of physiological and pathological processes, affecting the entire cardiovascular continuum of MI. Gal-3 is encoded by a LGALS-3 gene, located in a unique, 300 kb long haplotype block in Caucasians. Gal-3 serum level has been approved as a diagnostic marker for risk stratification and prognosis evaluation of HF patients according to the ACC/AHA/HFSA Guideline for the management of HF. The purpose of the present prospective study was to analyze the possible association of tag genetic variants of the haplotype block containing LGALS-3 with changes in cardiac parameters, LVEF and global radial strain (GRS), within 6 months post-MI. The study enrolled 120 patients with first acute MI that were prospectively followed-up 6 months after MI. According to Tagger server, rs4040064 G/T, rs11628437 G/A and rs7159490 C/T variants cover 82% (r2>0.8) of phenotypic variance of the aforementioned haplotype block. Tag variants were detected and genotyped by commercially available assays for allelic discrimination. Echocardiography examinations were performed at admission and 6 months post-MI. Change (Δ) of cardiac parameters was calculated as a difference between the value at 6-month follow-up and baseline value (at admission). The referent haplotype is set by the software for carrying haplotype association analysis and represents the most frequent haplotype in the studied groups. Bonferroni correction for multiple testing was performed and p values <0.025 were considered as statistically significant. We found that, compared to the reference GGC haplotype, GAT haplotype had significantly higher expected phenotypic mean [95% CI] of ΔGRS (3.77 [1.28 - 6.25] vs. −5.34 [−12.69 - 2.01], respectively, p = 0.025) and ΔLVEF (0.84 [−1.88 - 3.56] vs. −12.91 [−17.30 - −8.53], respectively, p = 0.00001), in the direction of decrease of GRS and LVEF 6 months after MI in patients bearing GAT haplotype.
Our findings suggest that GAT haplotype bears the risk for diminished LV transmural contractility and radial systolic function: In order to reach a definitive conclusion, our exploratory results should be further validated on a larger sample.