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Keywords: Cardiac repair, Immunomodulation, Pig model.

Background & Aim: Accumulating evidence supports the potential of extracellular vesicles (EVs) from mesenchymal stromal cell (MSC) as a therapy for cardiac healing after myocardial infarction (MI). Nevertheless, neither their efficient administration nor their therapeutic mechanisms are fully elucidated. Here, we evaluate the preclinical efficacy of a tissue engineering approach to locally deliver porcine cardiac adipose tissue MSC-EV (cATMSC-EV) in an acute MI pig model.

Methods, Results & Conclusion: Pigs (n=24) were subjected to MI by permanent ligation of the coronary artery. After 30 min, animals were randomized to Untreated or treated groups, who received a tissue engineered graft composed of a decellularized pericardial scaffold filled with peptide hydrogel and cATMSC-EV purified by size exclusion chromatography (EV-treated group) or buffer (Control group), placed over the post-infarcted myocardium. Cardiac troponin levels were significantly improved with less ventricle dilatation in the EV-treated group or buffer (Control group), placed over the post-infarcted myocardium. Cardiac troponin levels and cardiac MRI revealed consistent induction of myocardial damage and infarct size in all animals. After 30 days, cardiac function was significantly improved with less ventricle dilatation in the EV-treated group, indicating less myocardial remodelling. MRI showed reduced scar size in EV-treated animals, correlating with a decrease of fibrosis in the distal area (0.61±0.20 Collagen I area in Untreated vs 0.63±0.25 in Control vs 0.35±0.20 in Treated animals; p=0.030) and increased vascular density in the infarct core (0.21±0.13 Isolcitin B4 area in Untreated vs 0.25±0.14 in Control vs 0.41±0.05 in Treated animals; p=0.019). Less macrophage infiltration (13.92±2.85 CD163+ area in Untreated vs 0.25±0.14 in Control vs 0.41%±0.09 in Treated animals; p=0.0257) and more anti-inflammatory phenotype (CD163+CD73+) were found in the infarct of treated animals (0.44±0.09 CD163+CD73+ cells per field in Untreated vs 1.91±1.70 in Treated animals; p=0.0367). Surprisingly, local delivery of cATMSC-EV also triggered a systemic effect, reducing PBMC increase 1.91±1.70 in Treated animals; p=0.0367). 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.

These results highlight the clinical potential of cATMSC-EV combined with tissue engineering to modulate key features of ischemic injury and promote cardiac repair after MI.

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Exosomes

Administration of Amniotic Fluid Derived Extracellular Vesicle Is Associated with Decreased CRP in COVID-19 Patients

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Keywords: Extracellular Vesicles , COVID-19, Clinical Investigation.

Background & Aim: A human coronavirus (HCoV-19) has caused the novel coronavirus disease (COVID-19) outbreak worldwide. There is an urgent need to develop new interventions to suppress the excessive immune response, protect alveolar function, and reduce lung and systemic organ damage. Zofin is an acellular biologic that contains the soluble and extracellular vesicle fraction of human amniotic fluid. We have recently initiated single patient emergency/compassionate use eINDs for 12 subjects under our approved parent IND 19881. These trials included patients with various stages of COVID-19 infection and respiratory distress (mild to moderate ARDS, Post-COVID-19 complications, and Multi-organ failure in the ICU).

Methods, Results & Conclusion: Zofin contains 2.3×1011 particles/ml with 70-80% positive expression of exosome markers CD63 and CD81. Zofin was administered IV as 1ml doses (3-4 doses) within the first 3-4 visits. Scheduled visits were day 0,4,8,12,21, 28, and 60. If BMI was greater than 40, an additional visit was included at day 6 to administer an extra dose. The primary objective of these studies was to demonstrate the safety of Zofin while secondarily observing for efficacy by SOFA score assessment, chest X-Rays, and inflammatory biomarker testing.

The approved FDA IND numbers are as follows: eIND#5-IND#25426, eIND#1-IND#22370, eIND#2-IND#22371, eIND#3-IND#22897, eIND#4-IND#25426, eIND#11-IND#26776.

The clinical outcome of each patients has varied, depending on the severity and baseline clinical status. However, we have found an overall positive trend for a number of clinical improvements such as systemic inflammation (decreased CRP), organ failure scores for ICU patients, respiratory and fatigue improvements in outpatients. Importantly, there were no reported adverse events related to product administration or treatment in any of the treated patients.

This is the first demonstration of allogenic, amniotic fluid-derived extracellular vesicles as a safe and potentially efficacious therapeutic treatment for respiratory failure induced by COVID-19 infection.

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Immunotherapy: Malignant

Fludarabine-Exposure Predicts Disease Control Following CD19-Specific CAR T Cell (Tisagenlecleucel); A Report from Pediatric Real-World Car Consortium

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