Abstract: **P109**

**Human ESC-derived epicardial cells promote cardiomyocyte graft incorporation and function**

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Background: Cardiovascular medicine has fallen short of addressing the underlying problem of heart failure, which is a loss of contractile myocardium. Efforts to remuscularise failing hearts using human embryonic stem cell (hESC)-derived cardiomyocytes have been promising but limitations regarding graft size, cardiomyocyte maturation, proliferation and vascular supply remain. To overcome these shortcomings, we have made use of hESC-derived epicardium, which provides trophic and structural support during early heart development.

**Purpose:**
To enhance current cardiac repair strategies through maturation of hESC-derived cardiomyocytes.

**Methods:**
To define the ability of hESC-derived epicardium to mature hESC-derived cardiomyocytes, both cell types were co-cultured in collagen-based 3D-engineered heart tissues (3D-EHT) before assessing histological properties, Ca\(^{2+}\)-handling and force generation. To test the reparative capability of epicardial cells as a regenerative therapeutic in vivo 60 athymic rats underwent a 60-minute ischaemia-reperfusion injury prior to being randomly assigned to one of the following treatment arms by intramyocardial injection, 4 days following the injury: 1. hESC-epicardium, 2. hESC-cardiomyocytes, 3. hESC-epicardium+hESC-cardiomyocytes or 4. vehicle control. Cardiac ultrasound was performed at baseline, prior to cell transplantation and at 4 weeks, prior to post-mortem histological analysis.

**Results:**
HESC-derived epicardial cells result in maturation of cardiomyocytes in 3D-EHTs as testified by sarcomere length, cell diameter, cell size and ssTnl to cTnl isoform switch. Additionally, substantial functional enhancements were seen in 3D-EHTs containing epicardial cells, as measured by superior Ca\(^{2+}\)-handling and greater force generation when compared to mesenchymal stromal cells. In vivo, co-transplantation of cardiomyocytes with epicardial cells doubled cardiomyocyte proliferation, resulting in a 2.6-fold increase in cardiac graft size with superior graft properties compared to cardiomyocytes alone. Importantly, the observed epicardial-mediated histologic findings also translated to a greater increase in host cardiac function compared to controls either receiving cardiomyocytes or epicardial cells or vehicle only.

**Conclusion:**
The capability of epicardial cells to substantially enhance cardiomyocyte graft size and properties make them a potent adjuvant regenerative therapeutic for cardiac repair. Furthermore, this critically advances endeavours to mature stem cell-derived cardiomyocytes in vitro for tissue engineering applications, disease modelling and drug toxicity testing.