Abstracts

**Young Investigators Award**

**A THE ENDOTHELIUM AS A PARACRINE MODULATOR OF ADIPOSE FUNCTION: A ROLE FOR ENDOTHELIAL IGF-1R IN THE SETTING OF NUTRITIONAL OBESITY**

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In obesity the relationship between white adipose tissue expansion and neovascularisation becomes uncoupled leading to inadequate perfusion of adipose tissue. Under these circumstances the secretory profile of adipocytes becomes unfavourable and pro-atherosclerotic.

We hypothesised that reducing endothelial insulin like growth factor 1 receptor (IGF-1R) expression affects adipose tissue remodelling as a result of communication between endothelial cells and adipocytes.

To study the effect of endothelial IGF-1R deficiency, we developed a mouse with inducible endothelial specific IGF-1R deficiency (ECIGF-1RKD). In the context of diet induced obesity, ECIGF-1RKD mice were more insulin sensitive and had increased energy expenditure compared to littermate controls. ECIGF-1RKD mice also had favourable changes specific to the white adipose tissue, including; increased uncoupling protein-1 and vascular endothelial growth factor expression, enhanced endothelial sprouting and greater vascularisation.

The mechanisms underpinning the specific effect of endothelial specific IGF-1R deficiency on white adipose tissue were then explored in more detail. Lineage tracing experiments guided the need for alteration/addition of antihypertensive therapy.

**B OXIDIZED PKARI Protects Against Ischemia-Reperfusion Injury by Inhibiting Lysosomal-Triggered Calcium Release**

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Reperfusion-induced calcium overload profoundly affects the extent of myocardial injury following ischemia, impacting long-term morbidity and mortality. Reactive oxygen species play a crucial role in shaping the amplitude and spatiotemporal patterns of the intracellular calcium signal, but the mechanism governing this interplay remain unclear. Here we show that, in vivo, myocardial ischemia and reperfusion (I/R) potently induce formation of an intermolecular-disulfide within the type I regulatory subunits of protein kinase A (PKARI), both in mice and in humans. This conformation does not increase intrinsic PKA catalytic activity, but rather promotes AKAP-mediated subcellular compartmentalization of PKARI to the lysosome, where it inhibits calcium release from two-pore channels and prevents global calcium release from nearby ryanodine receptors. This regulatory mechanism is shown to be crucial for limiting I/R-induced cell death, as ‘redox dead’ Cys17Ser PKARI knock-in mice, which are incapable of undergoing Rlα disulfide formation, display substantially larger infarct sizes with concomitant reductions in left ventricular contractile recovery, both of which are prevented by inhibition of lysosomal calcium release at the time of reperfusion. These findings reveal a hitherto unknown role for PKARI, in its disulfide-activated state, to regulate calcium homeostasis and, in this way, potently protect the myocardium from post-ischemic injury.

**C IN-VIVO GRAFTING OF LARGE ENGINEERED HEART TISSUE PATCHES FOR CARDIAC REPAIR**

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Introduction Engineered heart tissue (EHT) strategies, by combining cells within a hydrogel matrix may overcome the limitations of intracoronary/myocardial cell delivery routes. EHTs regenerate heart muscle in small animal models but data
regarding clinically relevant engineered heart tissue (EHT) patches large enough for first-in-human studies are lacking.

Methods An up-scaled EHT patch (approx. 3 cm × 2 cm × 1.5 mm) consisting of 15–20 million human induced pluripotent stem cell derived cardiomyocytes (hiPSC-CM) embedded in a fibrin based hydrogel was developed. A rabbit myocardial infarction model was then developed to test for feasibility and efficacy of EHT grafting.

Results The patches began to beat spontaneously within 3 days of fabrication and after 28 days of dynamic culture (late EHTs) showed the development of several mature characteristics when compared to early patches (<14 days from fabrication). Late EHTs contained hiPSC-CMs which were more aligned; showed better contraction kinetics, and faster calcium transients.

We then tested the EHT patch in-vivo using a rabbit model. Patches were applied to infarcted hearts (n=14 [n=7 EHT vs n=7 sham]). Sham operations used non-cellular fibrin patches. Blinded echocardiographic analysis revealed a significant improvement in function in infarcted hearts that underwent EHT patch grafting (n=7; absolute difference of 10.04 ± 3.1% over sham group; fractional area change, P<0.01).

In-vivo telemetry recordings (n=5 MI/sham vs n=7 MI/ EHT) indicated that no clinically relevant arrhythmia was seen in the MI/EHT group and arrhythmia provocation protocols (ex vivo n=5 MI/sham vs n=6 MI/EHT) confirmed that the patch was not pro-arrhythmic (arrhythmia inducibility score 5.6 ± 1.0 [MI/patch] vs 5.0 ± 0.6 [MI/sham]; p=ns).

Conclusion An up-scaled clinically relevant EHT patch was developed and improved function in infarcted hearts without causing arrhythmia. Therefore EHT may have specific advantages over the direct intramyocardial injection of cells.