Soft Robotic Drug Delivery System Controls Delivery of VEGF to Stimulate Neovascularisation at an Islet Transplantation Site

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Background: Over 60% of islets transplanted in macrodevices are lost immediately post transplantation due to hypoxia from inadequate early vascularisation. Prevascularisation of an implant site by spatiotemporally delivering vascular endothelial growth factor (VEGF) is a potential solution. However, VEGF has a half-life of only 50 mins at body temperature if delivered systemically meaning multiple, large doses would be required which risk the formation of unstable, leaky blood vessels and adverse off-target effects. Our aim is to stabilise VEGF by electrostatically interacting with a carboxymethylcellulose-sodium alginate (CMC-SA) based hydrogel and loading into a soft robotic drug delivery (SRDD) device. Actuation of the SRDD device will release VEGF in a controlled manner with the aim of stimulating neovascularisation at an implant site for future islet transplantation.

Methods: *In vitro* release studies were performed to optimise an actuation regime for controlled release of Fluorescein isothiocyanate–Diethylaminoethyl–Dextran (Dextran), of the same charge and molecular weight as VEGF, from a CMC-SA based hydrogel loaded SRDD device. The SRDD system was submerged in release media, connected to the OB1 microflow system, actuated using a customisable actuation regime (MatLab®), and concentration of released Dextran determined using absorbance measurements. The actuation regime was modified until the optimal pressure, ramp, and cycle number were selected to facilitate controlled release of Dextran. Upon optimisation of the actuation regime, the SRDD device was loaded with CMC-SA based hydrogel without (N=8) or with (N=9) VEGF and implanted subcutaneously in female Sprague-Dawley rats. The SRDD system was actuated once daily for 7 days, then all rats were euthanised by CO_2 inhalation. The SRDD device and surrounding tissue were explanted *en bloc* and stained with CD31 and αSMA for histological analysis of angiogenesis.

Results: In the absence of mechanical stimulation, the passive release of Dextran was less than 0%. 6, 8, 10, and 12 psi released 0.78, 1.22, 2.68, and 1.68% Dextran, respectively. 10 psi was selected as the optimal pressure and ramp times were varied from 1-30 secs to further improve Dextran release. 1-, 3-, 5- ,10-, 20-, and 30 sec ramps released 3.85, 7.24, 17.17, 16.00, 14.44, and 20.64% Dextran, respectively. With 10 psi and a 5-sec ramp selected, a range of cycle numbers were examined. 2-, 3-, 5-, and 10 cycles released 4.56, 12.32, 40.98 and 53.61% Dextran, respectively. The optimised actuation regime consisted of 10 psi, 5 sec triangle ramp and 10 cycles. In preclinical studies, the controlled release of VEGF significantly increased CD31+ neovessels abundance ($p=0.0310$) and length density ($p=0.0310$) and significantly decreased radial diffusion distances ($p=0.0460$) compared to the no VEGF controls. VEGF also significantly increased the diameter of CD31+ blood vessels ($p=0.0130$). However, the percentage of αSMA+ blood vessels was not significantly increased ($p=0.3030$).

Conclusions: Actuation of our SRDD system was modifiable and facilitated controlled release of VEGF to stimulate neovascularisation at an implant site. Future preclinical studies will have an extended follow-up period to establish whether these neovessels persist and mature to prevascularise an implant site for future islet transplantation.