Transcutaneously refillable, 3D-printed biopolymeric encapsulation system for the transplantation of endocrine cells.

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Introduction

Cell transplantation holds great promise for the treatment of various endocrine, cardiovascular, and neurological pathologies. While autologous transplantation circumvents transplant rejection, poor vascularization, cell retention, and mechanical support still hinder successful engraftment. Furthermore, transplanted cells require a close interaction with the recipient’s vasculature not only to obtain adequate oxygen and nutrient supply, but also to respond to paracrine and endocrine cues essential for graft survival and function. To address this need, we developed a three-dimensional printed polylactic acid (PLA) cell encapsulation system termed *neovascularized implantable cell homing encapsulation (NICHE)*.

Experimental Method

3D printed NICHEs coated with platelet rich plasma (PRP) were subcutaneously implanted (Fig1A). After a 4 week pre-vascularization period (Fig1B), endocrine cells were transcutaneously loaded into the device (Fig1C). Retrievability of device was assessed at the end of the study (Fig1D).

Figure 1. Experimental set-up

Device Characterization

The NICHE has a diameter of 10 mm, a thickness of 2.5 mm, and a cell reservoir volume of 200 µl (Fig2A). To promote homogeneous cell distribution, the cell reservoir consists of square microchambers (300µm x 300 µm) connected to the subcutaneous tissue via an array of square micro-channels (100 µm x 100 µm) that allow vessel penetration and cell retention (Fig2B-D). To enhance vascularization, the NICHE was coated and filled with a PRP hydrogel capable of releasing growth factors (Fig2E-F).

Figure 2. Device characterization

Results

To assess tissue and blood vessel penetration, NICHEs were subcutaneously implanted in mice. One and two weeks post-implantation not much tissue had penetrated into the capsule (data not shown). By week four, NICHEs were filled with vascularized tissue suitable to home transplanted cells (Fig3A). Vascularization was confirmed with CD31 (green) and DAPI (blue) labeling (Fig 3B). A separate study conducted in rats, pigs, and rhesus macaques showed similar results (Fig3C).

Figure 3. NICHE vascularization

4-weeks pre-vascularized NICHEs were transcutaneously loaded with 2,000 IEQ human islets. Insulin release was detected for 12 weeks. A subsequent loading of additional islets (2,000 IEQ) produced an increase in insulin levels (~10 µIU/ml) for another 10 weeks, demonstrating viability of the transplant (Fig 4A). The NICHE was later adopted to transplant Leydig cells in castrated Rag-/- mice. Cells maintained viability and testosterone secretion achieving plasma concentrations between 1.5 ng/ml to 2.2 ng/ml (Fig4B). At week 14, H&E staining revealed extensive vascularization of tissue within NICHE (Fig4C-E). Labeling of Leydig cells with HSD3B (green) and DAPI (blue) confirmed cell permanence (Fig4F-H).

Figure 4. Evaluation of NICHE for endocrine cell transplantation

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Future Directions

We are currently developing the NICHE2 for allo- or xenografts, which allows for local, constant, and sustained immunosuppression.

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