Optimization of Oxygen Transport within Islet Macroencapsulation Device via Finite Element Modeling and MRI Oximetry

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Introduction: Type 1 Diabetes (T1D) is an autoimmune disease where insulin-producing beta cells within the pancreatic islet are destroyed. Allogeneic islet transplantation has the potential to restore beta cell function in patients with T1D. However, patients require long-term immunosuppression, and in most cases, the long-term risks of chronic immunosuppression are much greater than the risks associated with long-term T1D. Researchers have designed macroencapsulation devices to shield transplanted islets from the recipient immune system in an effort to eliminate immunosuppression. However, these devices often lack sufficient oxygen transport to support cell viability due to suboptimal geometry. A macroencapsulation device design with optimal geometry that minimizes diffusion distances is necessary to maximize graft survival and function. *We hypothesize that macroencapsulation device geometry optimized via modeling of device oxygen gradients will enhance islet function and survival within the macroencapsulation device.*

Materials and Methods: Finite Element Modeling (FEM): diffusion equation $[(\partial c_i/\partial t\} + \nabla\bullet(-D_i\nabla c_i) = R_i]$ models the mass transport of dissolved species in COMSOL. Islet oxygen consumption rates derived from the literature were evaluated in disks of varied geometry and cell density. Design and Fabrication of Injection Mold: Injection molds were 3D-printed to generate varied hydrogel macroencapsulation device geometries. INS-1E beta cells were encapsulated at a density of 5 IEQ/µL in 2% agarose or slow-gelling 2% alginate hydrogels in 1 mm and 2 mm diameter spiral geometries. Cell viability was evaluated at 0 and 24 hours via live/dead staining and at 24 hours via Alamar Blue. Human islets were encapsulated at a density of 20 IEQ/ µL in 2% agarose and slow-gelling 2% alginate hydrogels in 1 mm diameter spiral geometries. Cell viability was evaluated at 48 hours via live/dead staining, Alamar Blue, and Glucose Stimulated Insulin Response (GSIR). Validation of models: Hexamethyldisiloxane (HMDSO) nanoprobes used for evaluating oxygenation within macroencapusulation devices were encapsulated at varied densities (0%, 5%, 10%, 20%) along with INS-1E beta cells in a 2% agarose hydrogel of a 1 mm diameter spiral geometry and cultured under standard conditions. Encapsulated cell viability and nanoprobe cytotoxicity were evaluated at 48 hours via Alamar Blue and Live/Dead. Polydimethylsiloxane (PDMS) microbeads were fabricated using an emulsion technique as a potential method of incorporating HMDSO nanoprobes into various hydrogel macroencapsulation devices to further mitigate any cytotoxicity caused by the HDMSO nanoprobes.

Results and Discussions: Utilizing COMSOL FEM software, we generated a model of oxygenation within a cylindrical hydrogel macroencapsulation device of varied islet densities to determine each parameter's impact on oxygen gradients within the macroencapsulation device. To generate complex macroencapsulation geometries with improved oxygen transport, we developed a hydrogel injection mold technique. Human islet viability was evaluated in injection molded hydrogel spiral geometries with 1 mm diameters. The injection molding technique did not negatively impact islet viability in either the 2% alginate or 2% agarose gels. These observations are supported by live/dead imaging of spiral and cylindrical geometries with similar volumes (**Figure 1A**). We evaluated nanoprobe cytotoxicity within 2% agarose 1 mm diameter spiral hydrogels (**Figure 1B**) in order to validate oxygen levels in varied geometrical macroencapsulation designs via MRI oximetry. We fabricated PDMS microbeads to encapsulate HDMSO nanoprobes (**Figure 1C**) and characterized the size distribution of the PDMS microbeads using ImageJ software (**Figure 1D**).

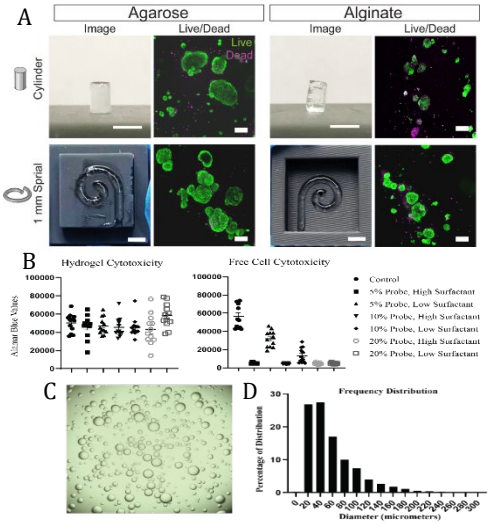

Figure 1. Live/dead imaging of 2% agarose and 2% alginate 1 mm diameter spirals with encapsulated human islets demonstrates no negative impact from injection molding process. Calcein AM (green) is live while Ethidium Homodimer (magenta) is dead. Scale bar for live/dead images is 200 µm and for hydrogel images 5 mm (A). Metabolic activity of insulin-producing beta cells was evaluated at 24 hours for cells with HDMSO nanoprobe freely in solution and for cells encapsulated with HDMSO nanoprobes (B). PDMS microbeads fabricated using emulsion technique. Scale bar is (C). Size distribution of PDMS microbeads measured using ImageJ (D).

Conclusions and Future Directions: Future experiments will evaluate islet function and viability in both syngeneic and xenogeneic models using the injection molds. We will evaluate oxygenation within in vivo constructs using HDMSO nanoprobes.