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Statement of Purpose: Diabetes is a global epidemic afflicting over 300 million people. While a rigorous regimen of blood glucose monitoring coupled with daily injections of exogenous insulin remains the leading treatment for type one diabetics, patients still suffer ill effects due to the challenges associated with daily compliance. The transplantation of donor tissue, either in the form of a pancreas transplantation or infusion of cadaveric islets, are currently implemented clinically as one strategy to achieve insulin independence for type 1 diabetics. This approach has been limited due to two major drawbacks: 1) the limited supply of available donor tissue, and 2) the adverse effects associated with a lifetime of immunosuppression. Recently, the *in vitro* differentiation of human pluripotent stem cells (hPSCs) into functional pancreatic β-cells has been reported, providing for the first time a path to produce an unlimited supply of human insulin-producing tissue. The immunoisolation of insulin-producing cells with porous biomaterials to provide an immune-barrier is one strategy to overcome the need for immunosuppression. However, clinical implementation has been challenging due to host immune responses to implant materials. Here, we report the first long term glycemic correction of a diabetic, immune-competent animal model with human SC-β cells encapsulated using a novel superbiocompatible chemically modified alginate formulation. Further we summarize our IND-Enabling results prepared for clinical translation.

Methods: To ensure proper biocompatibility assessment in our studies we used an immunocompetent streptozotocin-induced diabetic C57BL/6 mouse model for our study, because this strain is known to produce a strong fibrotic and foreign body response similar to observations made in human patients. Using a combinatorial synthesis and screening strategy we evaluated a large library of chemically modified alginate hydrogel formulation for in vivo biocompatibility. Lead formulation is then used for encapsulate SC-β cells and evaluated for ability to provide long-term glycemic correction and glucose-responsiveness in immune competent diabetic mice. Further biocompatibility assessment of cell loaded capsules were performed in non human primates.

Results: Here, we report the first long term glycemic correction of a diabetic, immune-competent animal model with human SC-β cells. SC-β cells were encapsulated with novel, alginate-derivatives capable of mitigating foreign body responses in vivo. Devices implanted into the intraperitoneal (IP) space induced glycemic correction in streptozotocin-treated (STZ) C57BL/6J mice until removal at 174 days without any immunosuppression. Human c-peptide and in vivo glucose responsiveness demonstrate therapeutically-relevant glycemic control. Retrieved implants revealed viable insulin-producing cells after 174 days in immune-competent mice. Evaluation of capsules loaded with cells in non human primates suggest that our lead capsule can protect maintain cell viability without immunosuppression.

Conclusions: We have shown that encapsulated SC-β cells can achieve glucose-responsive, long-term glycemic correction (174 days with the mice still euglycemic at the end of the experiment) in an immune-competent diabetic animal with no immunosuppression. This formulation provided sufficient immunoprotection to enable long-term glycemic correction, in spite of the xenogeneic stimulation that these human cells manifest in an immunocompetent rodent recipient. We believe that encapsulated human SC-β cells have the potential to provide for insulin independence for patients suffering from type 1 diabetes.

References:

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