# A Novel Arteriovenous Graft Platform for Pancreatic Islet Xenotransplantation

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**Hypothesis:** We hypothesized that implantation of alginate-encapsulated human pancreatic islets within a multilayered arteriovenous graft can protect islets from immunorejection, and facilitate functional pancreatic xenotransplantation in a living large animal host without the need for immunosuppression.

**Background:** Nearly 30 million Americans have diabetes, and its prevalence will continue to increase over the next several decades. Transplantation of pancreatic islets may be a lasting cure for diabetes; however, two major limitations have persisted: ***1)*** limited oxygenation of transplanted islets, and ***2)*** risk of immunorejection. To mitigate these limitations, we engineered a novel multi-layered arteriovenous graft (AVGRx) designed to facilitate xenotransplantation of pancreatic islets. The AVGRx central treatment chamber is sequestered by an outer transparent nylon barrier and an inner semi-permeable porous PTFE (pPTFE) membrane with a pore diameter of 0.2µm (Figure1A). The inner pPTFE layer is permeable to glucose, insulin, and oxygen, but not to immune cells. **Methods:** Human pancreatic islets were purchased from Prodo Laboratories, Inc. (Aliso Viejo, CA), and also isolated from human donor pancreas procured at Mid-America Transplant recovery facility (St. Louis, MO). Islets were encapsulated in alginate utilizing a custom 3D-printed droplet generator. Islet viability was confirmed using a calcein:ethidium homodimer-1 surface stain. Islet functionality was evaluated using a glucose stimulated insulin secretion (GSIS) assay. To assess AVGRx patency *in vivo*, 3 adult male Yorkshire porcine hosts underwent AVGRx implantation in a right internal carotid artery to external jugular vein configuration (Figure1B), survived, and were maintained on dual-antiplatelet therapy. Graft patency was confirmed with weekly ultrasounds. In 2 additional porcine hosts, the AVGRx treatment chamber was loaded with 100,000 IEQ alginate encapsulated human pancreatic islets, and no immunosuppression was administered. Human and porcine insulin levels were measured pre- and post-intravenous administration of 500 mg/kg dextrose boluses on Weeks 1 and 3 post-implantation. All porcine hosts were then euthanized for graft explantation and histological assessments. **Results:** There was ***100%*** patency of AVGRx over the study period in all porcine hosts (Figure1C). Dextrose boluses caused a rise in ***both human and porcine insulin*** in the porcine host serum up to Week 3 (Figure2A). Islets explanted from AVGRx at Week 3 stained for C-peptide and Nkx, remained with high viability, and produced insulin (Figure 2B, C, & D). **Conclusions:** Here we demonstrate the feasibility of the AVGRx as a platform for human pancreatic islet xenotransplantation in a porcine host over a 3 week period, ***without the need for any immunosuppression***. We believe this study provides the foundation for a commercial product that may provide a lasting cure for individuals with insulin-dependent diabetes.