

MR-guided engraftment of human pancreatic islet cells in a diabetic swine using immunoprotection with clinically applicable magnetocapsules.

D. R. Arifin^{1,2}, A. Arepally¹, T. W. Link^{2,3}, W. D. Gilson^{1,4}, V. A. Ferrari⁵, R. L. Wilensky⁵, D. L. Kraitchman¹, and J. W. Bulte^{1,2}

¹Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States, ²Cellular Imaging Section, Institute for Cell Engineering, Johns Hopkins University School of Medicine, ³Biomedical Engineering, Johns Hopkins University School of Medicine, ⁴Siemens Corporate Research, Inc., Baltimore, MD, United States, ⁵Cardiovascular Division, Hospital of University of Pennsylvania, Philadelphia, PA, United States

Introduction In the US alone, 23.6 million people suffer from diabetes, with 5-10% of them having type 1 diabetes¹. A potential long-term treatment of type 1 diabetes is transplantation of donor pancreatic cells. Microencapsulation of pancreatic cells offers immunoprotection for engrafted cells while allowing insulin and metabolites to diffuse across the membranes, thereby eliminating or reducing immunosuppressive therapy.

Methods Human pancreatic islet cells were encapsulated in novel alginate beads gelled by Ba²⁺, crosslinked with clinical-grade protamine sulfate and further crosslinked with a final layer of alginate. Ten percent (1 ml of Feridex per 9 ml of alginate) of Feridex was co-encapsulated in the capsule core enabling negative contrast MRI of transplanted capsules. The magnetocapsules were synthesized with one human islet per capsule. Diabetes was induced in a Yorkshire pig with intravenous injections of streptozotocin (125 mg per kg)². To maintain its blood glucose levels, the swine received daily injections of porcine insulin (Vetsulin) on a sliding scale. Using a MR-compatible catheter³, 140,000 magnetocapsules (containing a total of 1 ml of Feridex) were infused into the portal vein of the swine. A 1.5T clinical MR scanner (Espree, Siemens AG) was used to monitor correct liver engraftment and to visualize magnetocapsule distribution in the liver as hypointensities. Engraftment procedure was successfully performed on two pigs. The imaging protocol was: a 3D volume interpolated breath-hold (VIBE) examination based on a 3D Flash sequence with fat saturation (TR=6.81 ms, TE=2.4 ms, matrix=256×240, FOV=360×337, and slice thickness=2.5 mm). Gadopentetate dimeglumine (30cc, Magnevist, Berlex) was injected IV followed by post-contrast imaging after a 30 seconds delay.

Results Transplanted human pancreatic islets were viable and functional *in vivo* for at least 14 days post-engraftment as indicated by human C-peptide levels of 12-46 pg/ml (Figure 1). The levels of human C-peptide and porcine insulin were similar, indicating that the engrafted human islets, surviving endogenous pancreatic islets (not destroyed by streptozotocin) and exogenously administered porcine insulin simultaneously functioned to regulate the blood glucose levels of the swine. The swine was independent of Vetsulin with a blood glucose <300 mg/dl for two days (Figure 2). Magnetocapsules engrafted in the livers of both pigs were clearly visualized as hypointensities. Representative MRIs of one swine are shown (Figure 3).

Conclusions We demonstrate the potential of cadaver human pancreatic cells immunoprotected inside novel alginate/protamine sulfate/alginate magnetocapsules to treat type 1 diabetes in a large animal model, providing a means to noninvasively monitor transplantation of cells in real-time using MRI. A larger number of engrafted pancreatic cells will likely be required to completely treat and cure a diabetic swine.

References 1. American Diabetes Association (2008).

2. Mohler, E.R. *et al. Arterioscl. Throm. Vas.* **28** (5), 850-855 (2008).

3. Sathyaranayana, S. *et al. J. Magn. Reson. Imaging* **26** (2), 386-391 (2007).

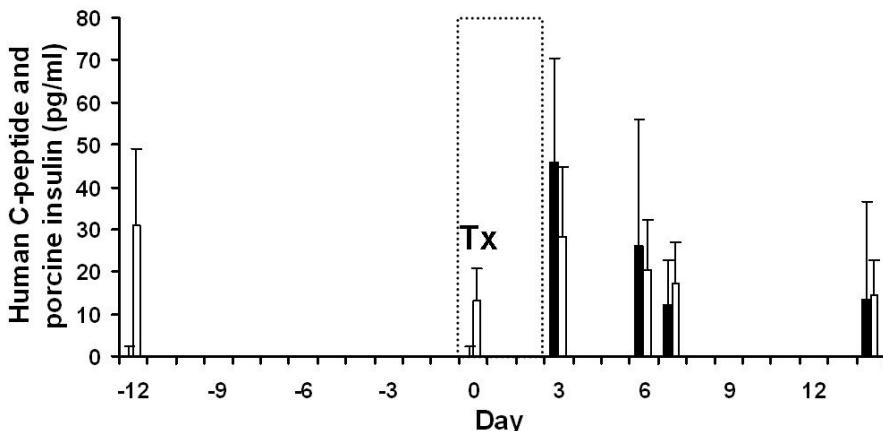


Figure 1. Human C-peptide levels (black bars) in a diabetic swine before and after engraftment of magneto-encapsulated human pancreatic islets on Day 0, and porcine insulin levels from surviving endogenous islets and Vetsulin (white bars). Tx = transplantation. Dotted area: Diabetic swine was independent of Vetsulin for 2 days post-engraftment.

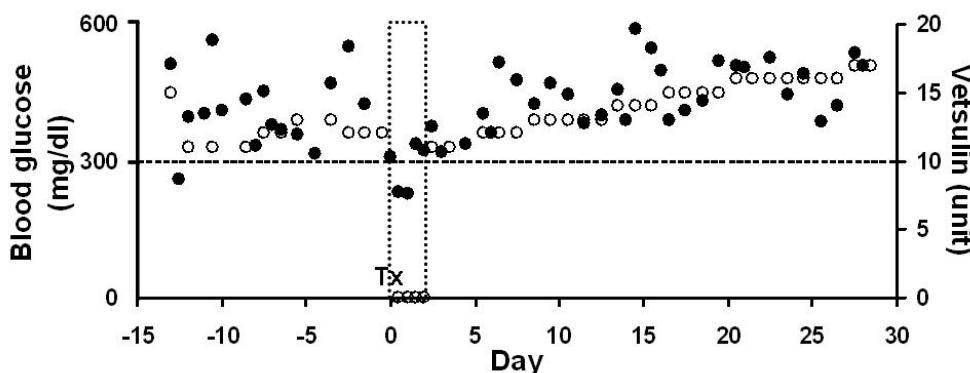


Figure 2. Blood glucose levels (●) of a diabetic swine and doses of administered Vetsulin (○) before and after engraftment of magneto-encapsulated human pancreatic islets on Day 0. Tx = transplantation. Dotted area: Diabetic swine was independent of Vetsulin for 2 days post-engraftment. The target blood glucose level was <300 mg/dl.

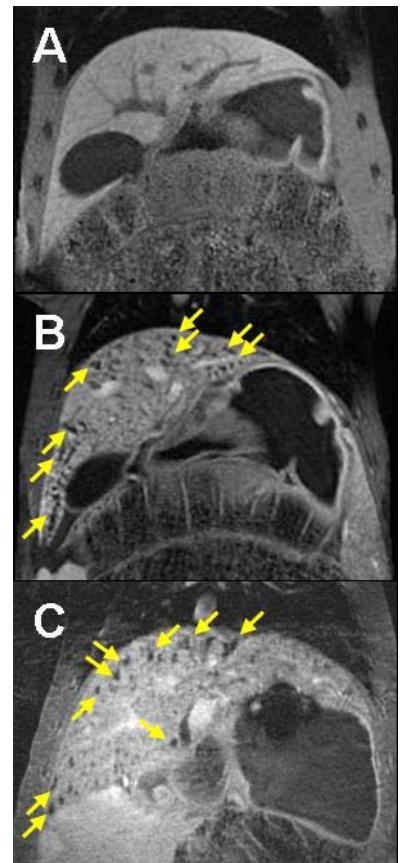


Figure 3. 1.5T coronal MR images of a swine liver before (A), 10 minutes (B) and 1 month (C) after transplantation of magnetocapsules. Capsules appeared as hypointensities (indicated by arrows).