Novel Trimodal Gadolinium-Gold Microcapsules for Simultaneous Immunoprotection and Positive Contrast MRI, X-ray, and Ultrasound Imaging of Human Pancreatic Islet Cells.

D. R. Arifin[1,2], C. Long[1,2], A. A. Gilad[1,2], S. Manek[2,3], E. Call[2], C. Alric[4], S. Roux[4], O. Tillement[4], T. W. Link[2,3], A. Arepally[1], and J. W. Bulte[1,2]

[1]Radiology and Radiological Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, United States, [2]Cellular Imaging Section, Institute for Cell Engineering, Johns Hopkins University School of Medicine, [3]Biomedical Engineering, Johns Hopkins University School of Medicine, [4]Laboratoire de Physico-Chimie des Materiaux Luminescents, Universite Claude Bernard Lyon 1, Lyon, France

Introduction Transplantation of donor pancreatic cells is currently the most promising long-term treatment of type I diabetes mellitus. Encapsulating pancreatic cells inside semi-permeable, biocompatible microcapsules offers immunoprotection for both transplanted cells and host while allowing insulin to diffuse out of the microcapsules.

Methods Pancreatic islet cells and novel gold nanoparticles functionalized with DTDTPA:gadolinium chelates (GadoGold) were co-encapsulated inside alginate/protamine sulfate/alginate microcapsules. Approximately 1.3 mM Gd^{3+} and 11.4 mM gold were encapsulated enabling trimodal imaging of the capsules: positive contrast MRI (Gd-enhanced), X-ray (gold providing radio-opacity) and ultrasound imaging (gold-US reflection). MR imaging was performed at 9.4 Tesla using a horizontal bore magnet and a 35 mm coil, X-ray imaging using a micro-CT scanner, and ultrasound imaging using a 40 MHz imager. Microcapsules were MR-imaged using T1-W and T2*-W gradient echo sequences. T1-W parameters for saline phantoms were: TR=500 ms, TE=14.1 ms, FOV=1.6×1.6 cm, matrix 256×256, slice thickness (ST)=1 mm, number of averages (N)=24. T2*-W parameters were the same except that TE=6.7 ms and N=12. T1-W parameters for mice were: TR=500 ms, TE=14.1 ms, FOV=2.4×1.8 cm, matrix 256×192, ST=0.8 mm, N=20, with fat suppression.

Results Human pancreatic islets encapsulated in GadoGold microcapsules were viable and functional for at least 5 days post-encapsulation as indicated by C-peptide secretion levels of 0.8-1.2 ng/islet/day *in vitro* (Figure 1). Blood glucose levels of diabetic mice transplanted with mouse βTC6 insulinoma cells immunoprotected inside GadoGold microcapsules recovered to the levels of healthy mice 7 days post-transplantation (Figure 2). Mice with blood glucose higher than 300 mg/dl were considered diabetic. GadoGold microcapsules in saline solutions (Figure 3) and in mice (Figure 4) were readily imaged with MRI, micro-CT scanner and ultrasound imaging, demonstrating the trimodal visibilities of GadoGold microcapsules *in vitro* and *in vivo*.

Conclusions This study demonstrates that cell encapsulation with gadolinium/gold nanoparticles has potential for pancreatic cell engraftment providing a means to non-invasively monitor the distribution and survival of transplanted cells in real time using MRI , X-ray and/or ultrasound imaging. We believe that this is the first report of imaging a single capsule exhibiting positive contrast at 9.4 Tesla; despite the high field strength a strong T1 effect can still be observed.

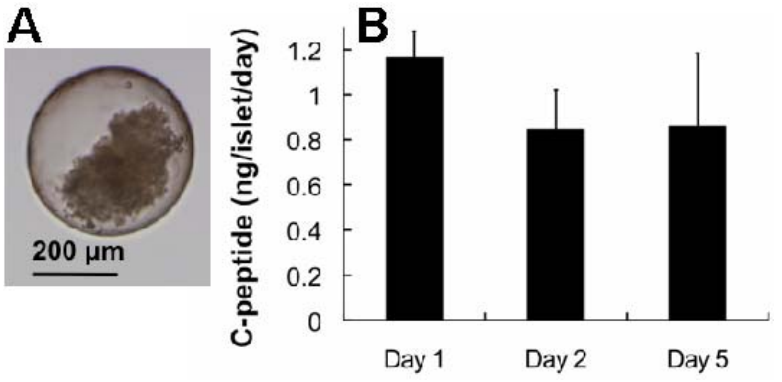

Figure 1. (A) A human pancreatic islet encapsulated inside a GadoGold microcapsule. (B) C-peptide secretion levels of human islets encapsulated in GadoGold microcapsules 1, 2 and 5 days post-encapsulation.

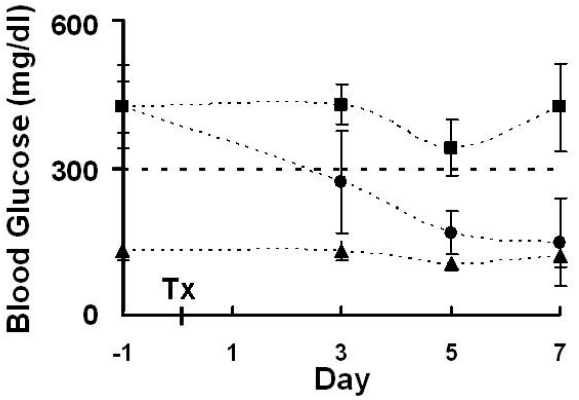

Figure 2. Blood glucose of diabetic mice with (●) and without (■) transplantation (Day 0) of mouse βTC6 insulinoma cells encapsulated in GadoGold microcapsules and blood glucose of healthy mice (▲). Tx = transplantation.

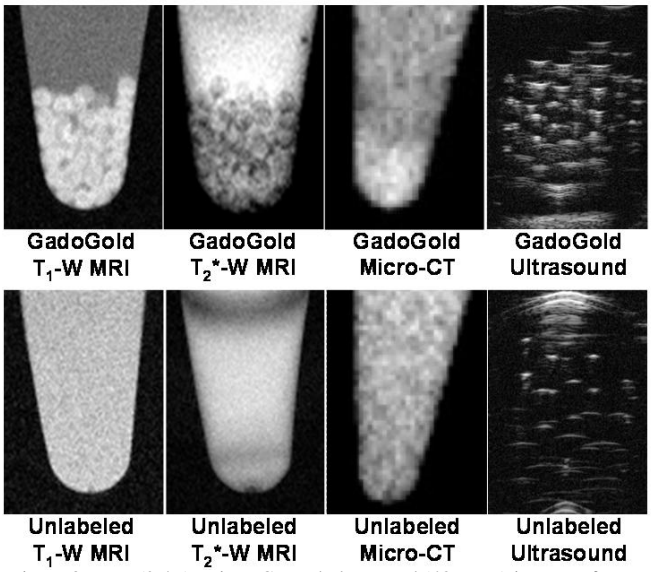

Figure 3. MRI (9.4T), micro-CT and ultrasound (40 MHz) images of GadoGold microcapsules in saline solutions at 1 day post-synthesis.

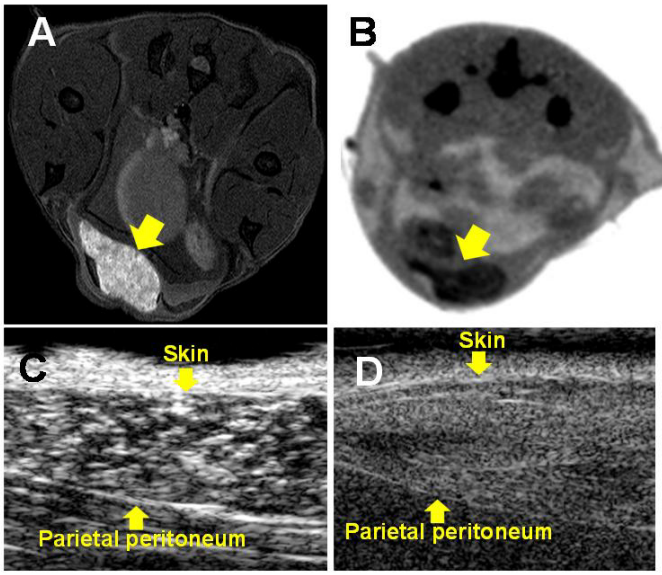

Figure 4. MRI (A) and micro-CT (B) images of GadoGold microcapsules subcut. injected in the mouse abdomen. US images of the fluid cavity between the abdomen skin and parietal peritoneum of a mouse with (C) and without (D) microcapsules.