**Functional Imaging of Pancreatic Islets**

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Type-1 diabetes results from a decrease in insulin production attributable to a decrease in pancreatic islet β-cell function. Research endeavors have focused on several alternatives for insulin supplementation, including transplantation of islets. Currently, there are no methods to non-invasively assess the function of these transplants. Assessing the location/functionality of transplanted islets currently relies on histological sectioning (post-mortem) and serum glucose sampling. The in-vivo identification of islet transplants, and direct imaging of their function, remains unrealized. We propose using manganese as an activation-based contrast agent to image islets. Upon glucose stimulation, manganese enters β-cells through L-type calcium channels providing function-specific contrast.

**Introduction:** Type I diabetes results from a decrease in insulin production attributable to a decrease in pancreatic β-cell function. The pathologies resulting from Type I diabetes have serious morbidity and mortality consequences. To overcome the decrease in endogenous insulin production, research endeavors have focused on several alternatives for insulin supplementation including implantable biocapsules containing insulinoma cells, and transplantation of intact pancreatic islets. However, there are currently no methods to non-invasively assess the function of these implants and transplants.

Previously our group has demonstrated manganese (Mn) enhanced MRI can be used to image activation of mouse insulinoma (BT2C) cells [1]. Manganese acts as a calcium analog and paramagnetic relaxation agent which upon glucose stimulation enters activated β-cells through L-type calcium channels providing contrast and a measure of cell activation. In low doses, Mn acts as a T₁ contrast agent, but with excess Mn accumulation, T₂ effects dominate, and Mn presence leads to T₂ contrast.

Islet transplantation research has progressed significantly and currently there are several ongoing clinical trials. Islets are transplanted through the portal vein and are distributed through the liver as a site for islet engraftment. Assessing the location and functionality of the islets is difficult and currently relies only on histological sectioning (post-mortem) and the return to normal serum glucose. The *in vivo* identification of the islet transplants, and direct imaging of their function, remains unrealized. Direct functional imaging of islets is central in understanding post-transplant viability and efficacy of therapeutic approaches.

**Methods:** Islets were isolated using the standard Ricordi method with minor modifications. The islets were exposed to a subtoxic dose of 200 μM MnCl₂ for 60 minutes in the presence of a) Control: low glucose (5 mM) b) Stimulated: high glucose (20 mM). The islets were then washed twice in PBS to remove extracellular Mn, placed in 20 mM glucose medium to decrease Mn efflux, and loaded into glass capillaries for imaging. Following imaging, representative islets were removed and histologically stained for viability and insulin production.

**Results:** Islets were isolated using the standard Ricordi method with minor modifications. The islets were exposed to a subtoxic dose of 200 μM MnCl₂ for 60 minutes in the presence of a) Control: low glucose (5 mM) b) Stimulated: high glucose (20 mM). The islets were then washed twice in PBS to remove extracellular Mn, placed in 20 mM glucose medium to decrease Mn efflux, and loaded into glass capillaries for imaging. Following imaging, representative islets were removed and histologically stained for viability and insulin production.

**Discussion:** The contrast image in Figure 1b shows that activated islets are darker than non-activated islets. This points to the dominance of T₂ relaxation effects of manganese accumulation in activated islets. Islets are more sensitive to glucose load than are insulinoma cells. The resulting T₂ contrast is very encouraging because it indicates that much lower, optimal doses of MnCl₂ can be used to obtain T₁-weighted images in which the activated islets will appear brighter on an MR image than non-activated islets, as is the case with the isolated insulinoma cells.

Long-term, periodic evaluation of beta cell function can be used to optimize implant parameters and conditions, and provide the promise of MR tagging of islets prior to transplantation. However, to tag the islets with Mn, a better understanding of Mn efflux from islets is required. The viability images show the ability of the islets to tolerate the Mn dose delivered.

**Conclusions:** We have successfully demonstrated high resolution functional imaging of intact islets. Islets are more efficient in calcium regulation and Mn uptake than insulinoma cells and can therefore be subject to much lower Mn doses in the future to obtain T₁-weighted functional images. We are currently working on understanding compartmental exchange and inner- and outer- sphere relaxation effects for Mn contrast in intact islets. Since the islets are transplanted into the liver, future work will include observing the effects of Mn on a collection of islets in the presence of hepatocytes. Such experiments will reveal information on the ability of Mn to provide activation-based differential contrast between islets and hepatocytes.

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