Implantable MR probe to non-invasively monitor a bioartificial pancreas *in vitro* and *in vivo* at 11.1T

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Introduction

One approach to cure diabetes is to implant insulin-secreting cells in a tissue engineered (bioartificial) pancreatic construct. Using NMR to non-invasively monitor an implanted construct can provide correlations between construct function and physiologic effects post-implantation. It also offers the possibility of assessing changes in construct function towards developing early markers of construct failure in advance of end-point diabetic effects, e.g., hyperglycemia.

Previous studies showed great promise [1,2], however, the NMR imaging and spectroscopic techniques used need improvement. In order to achieve better sensitivity, an inductively coupled coil system has been developed (Fig. 2). This system includes an implantable loop-gap resonator inductively coupled to an external coil and run on an 11.1-T horizontal 40-cm clear-bore Magnex magnet equipped with a Bruker Biospec console for ^{1}H detection.

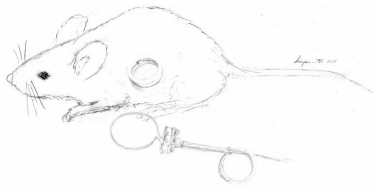

Figure 2: Inductively coupled coil system and its setting for *in vivo* experiments. The internal coil is implanted in an animal and surrounds the cells of the bioartificial pancreatic macroconstruct as presented on Figure 1. The external coil is placed near the implant to allow the two coils to couple.

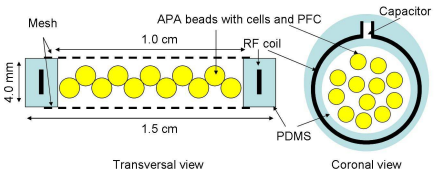

Figure 1: Coil-construct assembly schema. The macroconstruct consists of a coil surrounded by PDMS and containing Alginate/Poly-L-lysine/Alginate (APA) beads with βTC-tet cells and perfluorocarbonate (PFC). The beads are held in place by meshes placed on top and bottom of the PDMS ring.

Furthermore, to optimize the coil performance, reduce strong couplings with conductive biological tissues and fluids, and avoid potential immune responses from the host after implantation, the implantable coil must be coated with a material of low dielectric constant (to eliminate electric field storage) and low conductivity (to minimize the disturbance of the magnetic field generated by the coil). Otherwise, the resonant frequency of the coil will shift significantly and its quality factor decrease. The coating must also be soft and flexible as it will surround the construct and will be directly in contact with body tissue when implanted *in vivo*.

Methods

Simulations using GNEC Antenna Analysis software version 1.1 (Nittany, Inc. Riverton, UT) assisted in the design of the coil system. Once built, polydimethylsiloxane (PDMS) elastomer (biomedical grade, Factor II, Inc., Lakeside, AZ) was selected to coat the implantable coil because of its low dielectric properties and its uncomplicated handling compared to available biocompatible coating materials. A coating thickness of 1 mm allows the assembly to fit into the mouse peritoneal cavity yet maintain the coil performance. To evaluate the impact of the coating material and loading on the coil performance, the resonant frequency of the implantable coil and its quality factor (Q) were monitored. Their changes were measured using a vector network analyzer HP 8752C (Hewlett Packard, Santa Rosa, CA) and two probes in a loose coupling setting. The effect of the coating was further assessed by testing different but identical coils immersed in cell culture media, mimicking an *in vitro* environment.

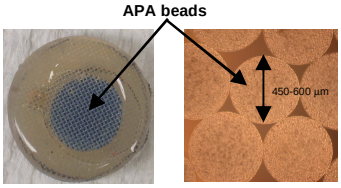

Figure 3: Photographs of a bead-loaded coil construct and the entrapped cells. (a) Macroscopic view of APA beads (colored in blue) placed in the construct. (b) Microscopic view of the cell-containing APA beads.

Implanted coils with a 1-mm-thick coat were tested in the magnet when coupled to the external coil using a phantom mimicking the mouse abdomen dielectric properties [3]. NMR measurements were performed using a spin-echo pulse sequence (TR=1000 ms, TE=10 ms, 1-mm slice, 1 average) with a 4-cm-by-4-cm field of view. The signal-to-noise ratio was calculated from the image obtained in three orthogonal directions then averaged.

In parallel studies, βTC-tet insulinoma cells were entrapped in alginate/poly-L-lysine/alginate (APA) beads. These beads were inserted within the coil-construct assembly (Fig. 3) directly after manufacture. The impact of the coil on the cells, and the impact of the cell environment on the coil and coating were examined over time via glucose and lactate measurements. NMR images were also acquired. Some coil-construct assemblies (Fig. 4) were loaded with cell-free APA beads and embedded in the abdomen phantom to optimize NMR techniques towards eventual *in vivo* application.

Results and Discussion

When an uncoated implantable coil was immersed in a tissue equivalent solution, the coil resonant frequency shifted severely and the quality factor fell to zero. With a 1-mm coating the implantable coil resonance frequency shifted by 40.5 ± 1.5% MHz from its original resonance frequency when immersed in cell culture media or tissue equivalent solution. The quality factor decreased by a factor of 29.4 ± 11%. To create the coupled coil system, the implantable coil frequency shift had to be taken into account. The quality factor of the whole loaded system decreased by a factor of 10.6 ± 2.3%.

Inductively coupled coils were found to be superior to surface coils by a factor of 4 even when loaded and coated with a 1-mm PDMS. With a gain of approximately 2.6 times when going from 4.7 Tesla to 11.1T, the net gain of the method presented here is about 10.5 times.

In vitro studies with coated coils filled with APA cell-containing beads demonstrate that entrapped cells can be kept alive for over a month, indicating that the coil design is appropriate to maintain cell viability for future *in vivo* applications.

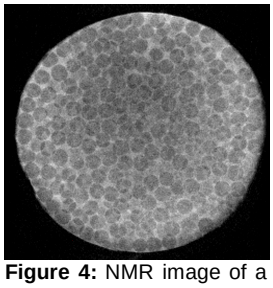

Figure 4: NMR image of a coil-construct assembly containing cell-free APA beads using a spin echo sequence (TR=7500 ms, TE=11.2 ms, 1-mm slice, 1 average).

Conclusions

The implantable inductively coupled coil system was successfully constructed, coated, integrated with the macroconstruct, and used to image the bioartificial pancreas in *vitro*. Moreover, this coil system showed a 10.5-time improvement in sensitivity compared to the use of a surface coil at 4.7T. Ongoing work is now focused on 1) fully characterizing this coil system *in vitro* and *in vivo* for ^{1}H detection, 2) studying the construct *in vitro* over time using NMR imaging and spectroscopy, and 3) further developing the system to achieve a multiple frequency system. A multiple frequency system will allow for simultaneous detection of nuclei (e.g., ^{1}H, ^{19}F, ^{31}P) important in monitoring the viability and the metabolic activities of cells encapsulated in the constructs.

References [1]. Stabler CL, *et al.* Tissue Eng. 11(3-4):404-414, 2005. [2]. Stabler CL, *et al.* Cell Transplant 14(2-3):139-149, 2005.
[3]. Beck BL, *et al*. Concepts Magn Reson B Magn Reson Eng 20(1):30-33, 2004.

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