MR Imaging and Spectroscopy of a Bioartificial Pancreas *In vitro* and *In vivo* at 11.1 T Using Implantable Probes

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Introduction

One approach to cure diabetes is to implant insulin-secreting cells within 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. NMR 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 to monitor insulin-secreting macroconstructs 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. 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.

After coating the coil to allow its use *in vitro* and *in vivo*, the construct was integrated inside the coil cavity (Fig. 1). This coil-construct assembly was then tested and optimized for *in vitro* and *in vivo* studies after implantation in a mouse peritoneal cavity.

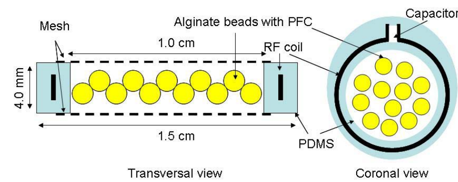

Figure 1: Coil-construct assembly schema. The macroconstruct consists of a coil surrounded by PDMS and containing alginate beads with perfluorocarbonate (PFC).

Methods

Implantable loop-gap coils were coated with a 1-mm-thick biomedical grade polydimethylsiloxane (PDMS) layer to allow their use *in vitro* and *in vivo*. A 300-µm-opening polyetheretherketone (PEEK) mesh was added on each side of the coated coil to create the construct cavity (Fig. 1). This cavity was filled with 0.3 mL of alginate beads (Alginate/Poly-L-lysine/Alginate (APA) or Barium/Alginate (BaA) beads). The diameter of the beads was between 400 and 600 µm.

Coil-construct assemblies were properly cleaned and sterilized before receiving blank beads (Fig.2a). Some assemblies were tested in the magnet when coupled to the external coil using a phantom mimicking the mouse abdomen dielectric properties [3]. Others were implanted in the peritoneal cavity of a mouse via a minimally invasive 2-cm celiotomy.

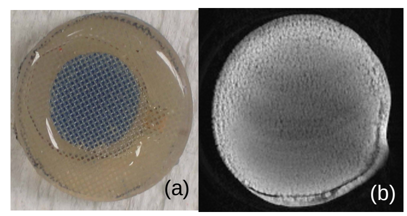

Figure 2: (a) coil-construct assembly with blue-colored beads within the cavity; (b) NMR image of the cavity containing cell-free BaA beads *in vivo* with an in-plane resolution of 78 µm.

NMR measurements were performed on both the phantoms and the mice using a spin-echo pulse sequence (TR=1000/2500 ms, TE=10 ms, 1-mm slice, 1 average) with a 4-cm-by-4-cm field of view (Fig. 2b). A mouse holder and a conventional gating procedure were used for the *in vivo* imaging. The signal-to-noise ratio was calculated from the average of images obtained in three orthogonal directions. A construct with the same characteristics as the assemblies but without the implantable coil was also tested using a surface coil only to compare and quantify the sensitivity improvement *in vivo*. Because of the morphologic discrepancies between animals, two different phantom settings were also used to reflect and quantify the difference of improvement when the distance between the implantable and external coils changes from 0.5 cm to 1 cm.

^{1}H spectroscopy was also performed on a 1mM Choline sample using a PRESS pulse sequence with a CHESS water suppression sequence (TR=2000 ms, TE=22 ms, 256 averages) on a 2-mm^3 voxel (Fig. 3). Furthermore, Perfluoro-[15]-crown-5-ether (PFCE) was introduced in the beads (up to 10%) and both ^{19}F images and spectra were acquired using a ^{19}F implantable coil system probe in phantoms (Fig. 4).

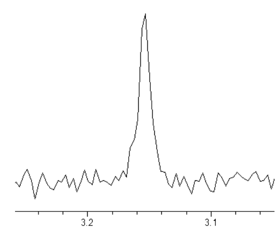

Figure 3: Choline spectrum on a 2-mm^3 voxel from a 1 mM sample acquired with a PRESS sequence.

Results and Discussion

Implanted coil-construct assemblies in phantoms resonated at 497.65 MHz (± 0.73 %), whereas assemblies implanted in the peritoneal cavity of a mouse resonated at 498.5 MHz (± 2.18 %). The quality factor of the implantable coil system was 14.14 (± 5.07 %) in the phantom and 19.7 (± 26 %) *in vivo*. Phantom studies have shown that the sensitivity improvement going from a surface coil to an implantable coil can vary from 2.61 (± 14.72 %) to 5.25 (± 17.54 %) when the distance between the two coils of the system varies between 0.51 (± 6.31 %) cm and 0.74 (± 8.46 %) cm. *In vivo* studies have shown that the sensitivity improvement of an implantable coil over a surface coil is 2.35 (± 13.27 %) when the average distance between the two coils of the system was 0.64 cm (± 24.38 %), including the average depth of implantation of 0.44 (± 24.38 %) cm and the 0.2-cm thick mouse holder. This improvement is to be added to the field strength improvement of 2.4 when going from 4.7T to 11.1T, in order to compare with our previous studies [1,2].

Choline spectra were acquired in less than 15 mins on 1-mM samples with an SNR over 16, which is very encouraging for future *in vivo* experiments (Fig. 3). ^{19}F images and spectra were acquired in less than 25 mins with an SNR greater than 45.

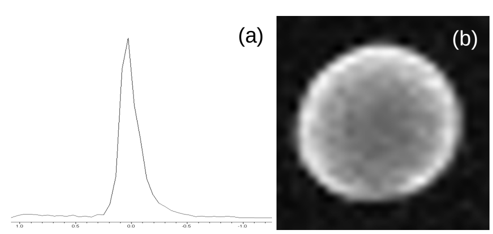

Figure 4: ^{19}F spectrum (a) and image (b) of 5% PFCE in APA beads *in vitro*.

Conclusions

The implantable inductively coupled coil system was successfully constructed, coated, integrated with the macroconstruct, and used to image the bioartificial pancreas *in vivo*. Moreover, this coil system showed a 6-fold improvement in sensitivity compared to the use of a surface coil at 4.7T. Ongoing work is now focused on 1) studying the construct *in vitro* over time using NMR imaging and spectroscopy, 2) further developing the system to make it receive-only and achieve a better localization for spectroscopy purposes, and 3) develop a multiple frequency system to 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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