Negative and Positive contrast strategies to track cell encapsulation devices post implantation

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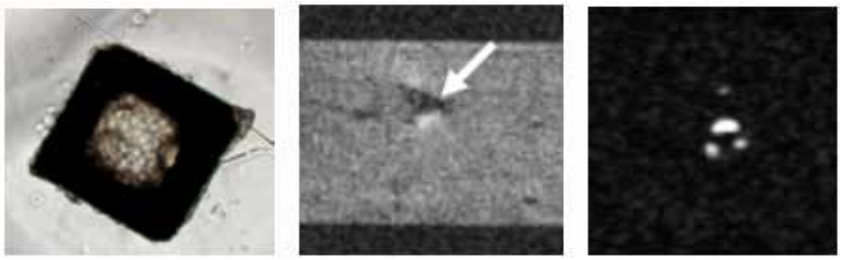
Introduction: Encapsulated cell therapy has shown promise in the treatment of diseases such as diabetes and hemophilia. However, currently cells are mostly encapsulated in polymer capsules and tracking the encapsulated cells post transplantation remains a challenge. Recently we have shown MRI tracking of diamagnetic, cubic cell encapsulating microcontainers (Fig. 1a), using strategies for both negative and positive contrast (1, 2). Here we show MRI tracking of pyramid microcontainers, using the Faraday shielding effect that results in signal loss within the microcontainer. The technique clearly allows us to obtain a signature MRI contrast of any of our arbitrarily shaped microcontainers used in encapsulated cell therapy. Additionally, we show positive MRI contrast of the cubic microcontainers with a simple chemical shift selective on-resonance water suppression technique, without the need for precise off-resonant signal excitation. This strategy allows us to distinguish the microcontainers from other sources of negative contrast and can be easily implemented on any research or clinical MR scanner.

Methods: All imaging was performed on an 11.7 T scanner with a Bruker Avance spectrometer equipped with triple-axis imaging gradients (300 G/cm maximum). Negative contrast images of a pyramidal copper microcontainer were obtained using a 3D FLASH sequence with the following acquisition parameters are TE = 5.3 ms, TR = 50 ms, flip angle = 30 degrees, field-of-view = 1.28 x 6.4 x 6.4 mm, acquisition matrix = 512 x 256 x 256, and 2 signal averages. Positive contrast images of a cubic copper microcontainer were acquired with a modified spin echo sequence with a chemical shift selective water suppression preparation. Briefly, a chemical shift selective 2 ms Gauss excitation RF pulse was proceeded by a 3 ms crusher gradient immediately prior to each spin-echo acquisition step; other acquisition parameters were TE = 4.2 ms, TR = 1000 ms, slice thickness = 0.25 mm, field-of-view = 3.6 x 3 6 cm, acquisition matrix = 64 x 40, and 8 signal averages.

Results and Discussion: The pyramid microcontainer was designed with a wall-thickness that was several times the skin depth of copper and was easily distinguished with MRI (Fig 1c). The pyramid geometry was maintained in MRI, clearly demonstrating that the contrast arose from the Faraday shielding effect and not a susceptibility effect. Positive contrast allows us to distinguish the microcontainers from other sources of signal void such as calcifications or motion artifacts. With chemical shift selective on-resonant water suppression, we ensured that only the shifted-frequency protons contributed to the signal. Positive contrast images of cubic microcontainers were obtained without the need for excitation of off-resonance signal in the proximity of the microcontainers (Fig. 1c), allowing easy implementation on MR scanners and circumventing problems associated with off-resonance excitation bandwidth limitations.

Conclusion: MRI tracking of arbitrarily shaped microcontainers was demonstrated. As compared with the cubic geometry, other shapes such as the pyramid provide a higher surface area-to-volume ratio and may therefore provide increased access of nutrients and oxygen to the encapsulated cells. We will further explore such geometries for our encapsulation devices. The negative- and positive- contrast non-invasive tracking can be used in conjunction with vascular and metabolic MR imaging to evaluate the physiological and biochemical environment proximal to the implant.



(a) (b) (c)

Fig 1: MDA-MB-231 breast cancer cells dispersed in an extracellular matrix gel and encapsulated in a cubic, copper microcontainer (a). MRI of a pyramid in a gel filled capillary reveals the pyramidal geometry, suggesting contrast from the Faraday shielding effect and not from the susceptibility effect (b). Positive contrast MRI of the cubic microcontainer in a gel-filled capillary provides images of the device in the complete absence of background signal (c).

References:

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