IN VIVO MR AND PET IMAGING OF A HIGHLY SENSITIVE POLYMERIC PARACEST CONTRAST AGENT

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Introduction

Chemical exchange saturation transfer (CEST) agents create contrast in MR images by exchanging their saturated lanthanide bound protons with those of bulk water **(1, 2)**. Saturation is achieved by applying a 5 to 10 second long broadband pulse, tuned to the CEST agent frequency, just before imaging. These agents have great potential to further extend the functional and molecular imaging capabilities of MR **(3)**. Some applications include measuring pH, angiogenesis, and glucose metabolism **(4, 5)**. Polymeric paramagnetic CEST (PARACEST) agents have recently been prepared by our group **(6)**. The polymeric agents increase the CEST effect by creating a higher concentration of lanthanide ions at the target site. These agents offer an order on magnitude improvement in sensitivity which greatly reduces *in vivo* dose levels. The improved sensitivity of the polymeric agents also helps overcome the magnetization transfer (MT) effect due to endogenous macromolecules in tissue, which can mask the CEST effect. We present the first *in vivo* images of a polymeric Eu^{3+} PARACEST agent using a simple fast spin echo pulse sequence. We also show that this agent could be used for simultaneous PET/MR imaging **(7)** by labeling the polymer with ^{64}Cu ($t_{1/2}$ = 12.7 h).

Materials and Methods

The Eu^{3+} polymeric PARACEST agent (Eu-Poly2(2%)) was prepared by a simple free-radical chain polymerization reaction with 2% initiator (w/w) resulting in a 17.4 degree of polymerization **(6)**. MR imaging was performed on a 9.4 T Varian system using a custom-made 25 mm diameter birdcage coil. A 0.1 mmol/kg dose of polymer (22 mM) was administered in 100 µL to a healthy mouse via jugular vein catheter. A fast spin echo pulse sequence was used (TR/TE = 75.6/9.1 ms, echo train = 8, average = 4) with a 5 second long, 10 µT saturation pulse for every TR. Each 128x128 pixel image took 6 minutes to acquire. A CEST image was created by subtracting the on-resonance image (saturation at 53 ppm) from the off-resonance image (saturation at -53 ppm). PET/CT imaging was performed on a Siemens Inveon small animal system. A 0.1 mmol/kg dose of polymer was administered in 100 µL to a healthy mouse via tail vein injection. The ^{64}Cu labeled Eu-Poly2(2%) had an activity of 120 µCi at time of injection. PET images were acquired at 5 minute intervals for 1 hour and showed the agent accumulating in the kidneys then clearing through the bladder.

Results

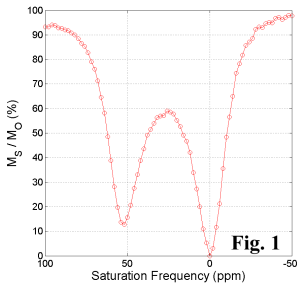
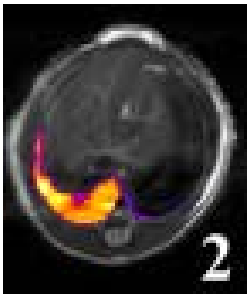
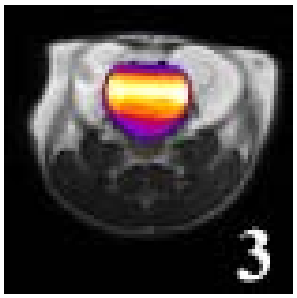
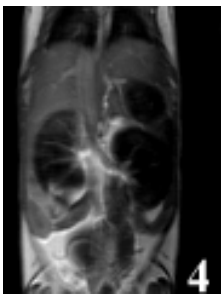


Fig. 1







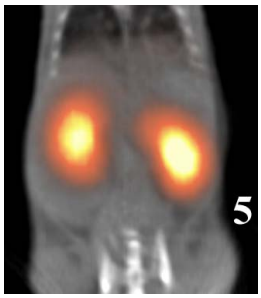


Fig. 1: *Ex vivo* z-spectrum of the Eu-Poly2(2%) agent at 22 mM concentration of polymer and 25 °C showing a strong 85% CEST effect at 53 ppm. **Fig.2:** Axial CEST image of the agent collecting behind the lungs in a pleural effusion. **Fig. 3:** Axial CEST image of the agent in the bladder at the end of a scan. **Fig. 4:** Coronal off-resonance image showing the darkening of the kidneys due to the uptake of the polymeric agent. **Fig. 5:** Coronal PET/CT image showing the uptake of the agent in the kidneys at 20 minutes past injection.

Conclusions

The first *in vivo* images of a polymerized Eu^{3+} PARACERST agent were obtained by fast spin-echo using a 5 second long, low-power (10 µT) saturation pulse. The injected dose of 0.1 mmol/kg is equivalent to that currently used for clinical Gd^{3+} contrast agents (e.g. Omniscan). The agent is non-toxic at this dose and has a prolonged blood circulation lifetime to help facilitate molecular targeting. A simultaneous PET/MR imaging agent can be created by labeling the Eu-Poly2(2%) with ^{64}Cu.

The darkening of the kidneys by the uptake of agent (**Fig. 4**), which inhibited CEST imaging of that organ, if not yet fully understood and is most likely due to a local T_2 shortening effect. Nonetheless, the increase in the CEST effect by the Eu-Poly2(2%) polymeric PARACEST agent allows it to be imaged *in vivo* using a simple fast spin-echo sequence. Even the CEST image from a failed tail vein injection (not shown) had a strong signal in the muscle at the base of the tail, proving that this agent can be imaged in regions where the MT effect is present.

References

(1) K. M. Ward, et al., J Mag Res, 143 (1): 79-87, 2000.
(2) S. Zhang, et al., JACS, 123: 1517-1518, 2001.
(3) R. Weissleder, et al., Radiology, 219 (2): 316-333, 2001.
(4) S. Aime, et al., MRM, 47: 639-648, 2002.
(5) J. Ren, et al. MRM, 60: 1047-1055, 2008.
(6) Y. Wu, et al., JACS, 130 (42): 13854-13855, 2008.
(7) C. Catana, et al., PNAS, 105 (10): 3705-3710, 2008.