Detection and Characterization of Europium based PARACEST contrast agents

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Introduction: Paramagnetic Chemical Exchange Saturation Transfer (PARACEST) works by utilizing an RF pulse at the chemical shift induced by the paramagnetic lanthanide to saturate a small pool of protons bound to the lanthanide complex. Exchange between this saturated proton pool and free protons in the surrounding bulk water causes a decrease in the overall water signal, resulting in a tunable negative MRI contrast. This type of contrast has been shown to have wide uses including the detection of small molecules [1][2][3][4], temperature [5], and pH [6][7]. Sensitivity to small concentrations of PARACEST agent would be useful to increase the potential for these and other studies. The purpose of this study is to show PARACEST contrast generation at a range of concentrations. To this end, imaging a phantom containing serial dilutions of a europium complex (Eu-DOTA-4AmC; Macrocyclics) from 100mM down to 0.4mM was completed at 14.6 T. A midrange concentration (8mM) was chosen to show viability of the contrast at pH's of 3, 7, 10 and 13; and temperature was varied between 14°C and 38°C (287 and 312 K) to demonstrate the change in CEST-spectra while maintaining contrast generation potential.

Methods: Phantoms of the europium complex (Eu-DOTA-4AmC; Macrocyclics) in water were imaged at a magnetic field strength of 14.6 T using spin-echo and gradient recall echo magnetization transfer sequences. To maintain a consistent level of RF power deposition, the CEST image was generated from the difference between two images, one with a positive offset value and the other with the negative offset value. Each individual image utilized a presaturation pulse consisting of 2000 3-lobe sinc or Gaussian pulses lasting 1 ms for a total irradiation time of two seconds. The offset value from bulk water for each set of images was varied between 0 and ±100 ppm.

Results and Discussion: Imaging results show a percent contrast of 85%, with a resulting contrast to noise ratio of 80 at the highest concentrations. The lowest concentrations resulted in a 2% contrast, with a contrast to noise ratio of 3. The results of the pH imaging illustrate a shift in the location of the optimal presaturation offset as a function of pH. The pH imaging also indicates a difference in magnitude of contrast at a given offset for different pH values, which has been shown in previous studies [7]. Contrast generation was achieved at pH's of 3, 7, and 10, but not at 13. The lack of contrast at the pH of 13 may suggest a pH dependant chemical change that prohibits the CEST in extremely basic conditions. CEST spectra from temperature studies indicate contrast generation potential at all tested temperatures ranging from 14°C and 38°C (287 and 312 K). The CEST spectra also show an increase in contrast generation at the lower temperatures. They illustrate a broader width of useful presaturation offsets at the higher temperatures, and a shift of the optimal offset with temperature. These results agree with previously documented effects of temperature on PARACEST agents [4], and are consistent with expectations of chemical exchange as a function of temperature. The overall results of this study show that at magnetic field strengths of at least 14.6 T, this PARACEST agent can generate contrast in a variety of pH and temperature environments, at concentrations down to 0.4mM.

Acknowledgements and References: All data were collected at the Advanced Magnetic Resonance Imaging and Spectroscopy (AMRIS) facility of the National High Magnetic Field Laboratory, at the University of Florida McKnight Brain Institute, Gainesville, FL. Eu-DOTA-4AmC was obtained from Macrocyclics, in Dallas, TX. [1] O. Vasalatiy et al., *Bioconjugate Chemistry*, vol. 19, Mar. 2008, pp. 598-606. [2] T. Chauvin et al., *Angewandte Chemie (International Ed. in English)*, vol. 47, 2008, pp. 4370-2. [3] R. Trokowski, S. Zhang, and A.D. Sherry, *Bioconjugate Chemistry*, vol. 15, pp. 1431-40. [4] B. Yoo and M.D. Pagel, *Journal of the American Chemical Society*, vol. 128, Nov. 2006, pp. 14032-3. [5] A.X. Li et al., *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, vol. 59, Feb. 2008, pp. 374-81. [6] S. Aime, D. Delli Castelli, and E. Terreno, *Angewandte Chemie (International Ed. in English)*, vol. 41, Nov. 2002, pp. 4334-6. [7] S. Aime et al., *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, vol. 47, Apr. 2002, pp. 639-48.

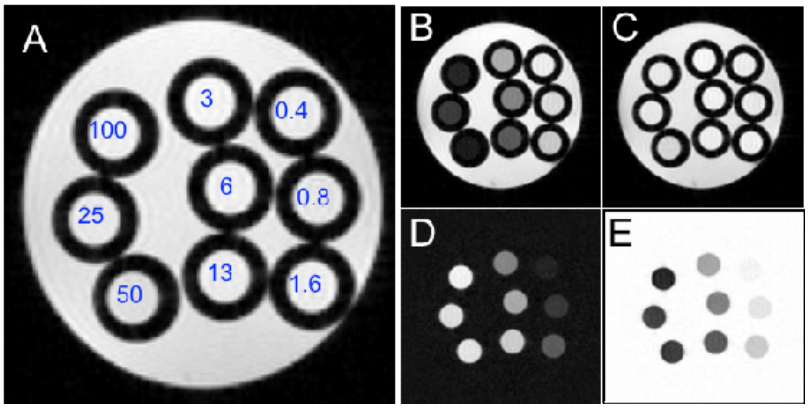

Figure 1. (Left) Serial dilutions imaged at 14.6 Tesla. A) Concentrations shown, ranging from 100 to 0.4mM. B and C) Images at positive and negative 53ppm respectively. D and E) Difference images taken as C-B and B-C respectively.

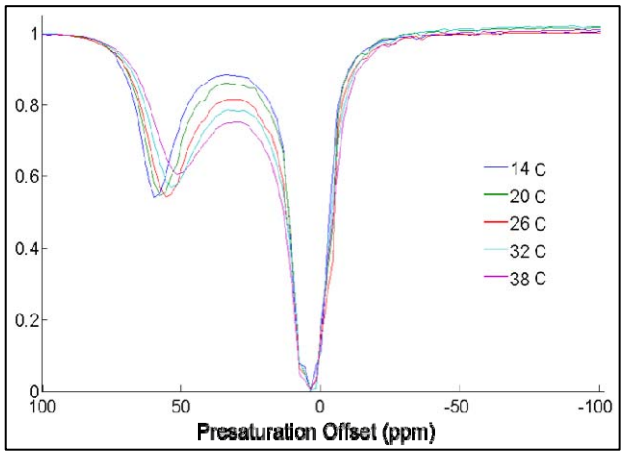

Figure 2. (Right) CEST spectra illustrating the contrast potential at all temperatures from 14°C to 38°C.

Figure 3. (Below) Image taken without presaturation, with pH's ranging from 3 to 13 labeled (lower left). The remaining images show the presence of contrast at the pH's of 3, 7 and 10. The presaturation offsets are shown in the lower corner of each image, and illustrate the shift of maximum contrast as a function of pH.