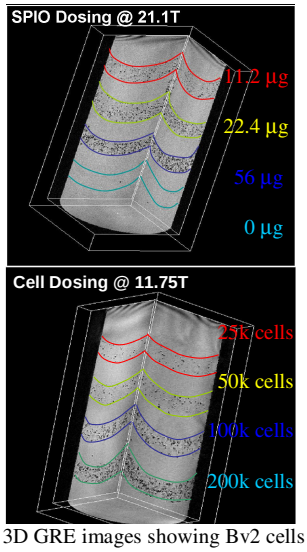
Intracellular MRI Contrast By SPIOs and Dy Chelates at 11.75 and 21.1 T

J. T. Rosenberg[1,2], J. M. Kogot[3], C. Ridel[3], G. F. Strouse[3], and S. C. Grant[1,2]

[1]The National High Magnetic Field Laboratory, Tallahassee, Florida, United States, [2]Chemical and Biomedical Engineering, Florida State University, Tallahassee, Florida, United States, [3]Chemistry and Biochemistry, Florida State University, Tallahassee, Florida, United States

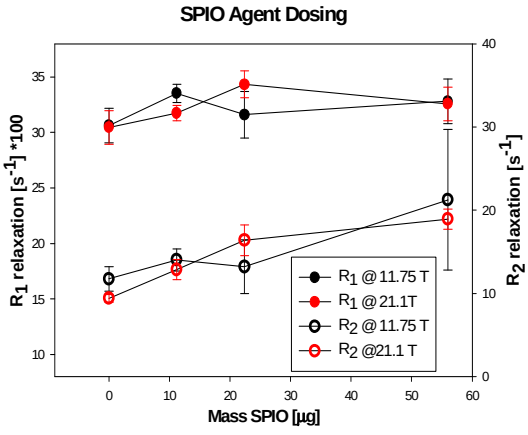
Introduction: The 21.1-T magnet at the National High Field Laboratory (NHMFL) [1] provides many new opportunities in MRI but also new challenges for exogenous contrast agents. MR contrast agents (CA) that are currently commercially available are limited in their effectiveness at high magnetic fields. For example, the effectiveness of Gd-based agents drops drastically with field strength [2]. In this study, we have used superparamagnetic iron oxides (SPIOs) and Dy chelates, both which should demonstrate increased relaxivity with higher field strengths, to examine uptake and contrast enhancement in neural microglia (Bv-2) as a function for two magnetic fields, 11.75 T (500 MHz) and 21.1 T (900 MHz).

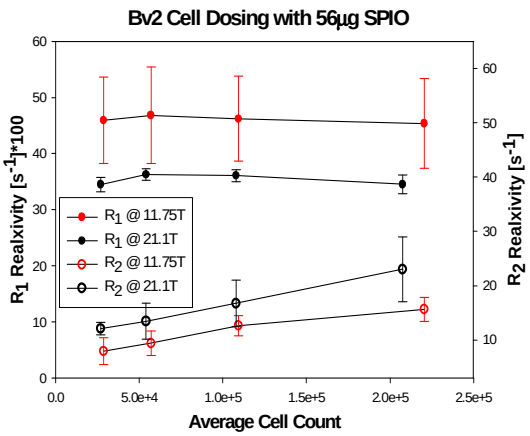
Methods: Bv-2 cells were incubated with either SPIO (Feridex, Bayer, Inc.) or Dy-DOTA ($DyCl_3$, Sigma conjugated with DOTA, Strem Chem., Inc) CAs for 6 hours before harvesting. Three washes were performed before trypsination to ensure that no agents were attached to the cell surface. Cells were immobilized in 1% agarose before imaging. In separate experiments, the effects of contrast agent dosing (100k cells were incubated with either 11, 22 and 56 µg of CA) and cell dosing (agarose layers were formed with either 25k, 50k, 100k or 200k cells incubated with 56 µg of CA) were examined. All data were acquired with a 21.1-T 900-MHz ultra-widebore (UWB) magnet (NHMFL) and an 11.75-T, 500-MHz widebore magnet (FAMU-FSU Engineering). For T_1 and T_2 measurements, a single-slice 2D spin-echo (SE) sequence was used with TRs and TEs varied, respectively. For T_2* measurements, TEs were varied in repeated acquisitions of a single-slice 2D gradient-recalled echo (GRE) and a 3D GRE.



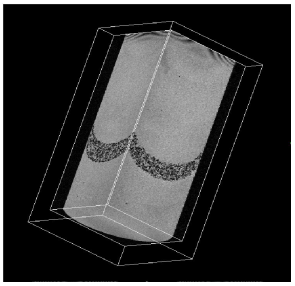
3D GRE images showing Bv2 cells immobilized in 1% agarose

Results and Conclusions: For SPIO agent dosing, there is not a significant difference in relaxation (either R_1 or R_2) between 11.75 and 21.1 T. An increase in contrast with increasing SPIO exposure is only seen in R_2. These results are echoed by SPIO-labeled cell dosing measurements at both fields that display increasing R_2 contrast with increasing cell counts, even though R_1 is constant regardless of the cell number. Cell dosing also displays differences between field strengths. These findings suggest that there is a limit to either SPIO uptake and/or contrast efficacy in Bv-2 cells, both possibly due to the method of endocytosis and cytoplasmic transport/sequestration. ICP-MS measurements display increasing intracellular iron content per cell with SPIO agent dosing. Because R_2 relaxation does not mimic the actual SPIO content per cell, these data suggest limited correlations between intracellular SPIO loading and actual MR contrast/quantification for Bv-2 cells at higher fields. On the other hand, Dy chelates (particularly Dy-DOTA as opposed to Dy-DTPA) show more contrast when Bv-2s are exposed to a concentration (16 µg/µL) similar to that of SPIOs (11 µg/µL). The positively charged DOTA-molecule may better stimulate phagocytosis, and the high field performance of Dy chelates on relaxation may outperform SPIOs at 21.1 T. These findings may impact the choice of intracellular contrast agent for high field studies that address the fate and transport of implanted cell lines, such as exogenous immune and stem cells.





Dy-DOTA & -DTPA @ 21.1T



3D-GRE of Bv2 cells loaded w/ Dy-DOTA/DTPA. Dy-DOTA showing increased contrast. T1/T2=2800/28 ms

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[1] Fu R *et al* J Magn Reson 2005:177:1-8. [2] Woods M, *et al* Dalton Trans 2005:(24):3829-3837.