

## MRI of cells and mice at 1 and 7 Tesla with Gd-targeting agents: when the low field is better!

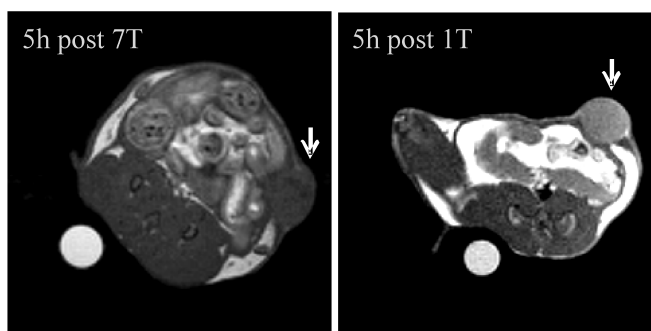
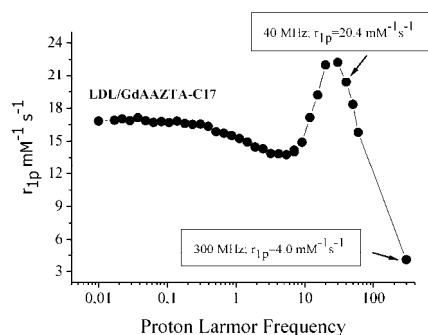
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**Introduction.** In respect to other molecular imaging modalities such as PET or SPECT, the low sensitivity is the main limitation of the Magnetic Resonance-Molecular Imaging (MRMI) probes. Therefore, the success of a MR-Molecular Imaging protocol strongly relies on the amplification effects associated to the accumulation of the agents at the pathological site. To this purpose the use of nanoparticles as carriers for MRI contrast agents (CA) has both the advantage to transport a high number of CA units at the site of interest and an improved efficiency of their contrast enhancement properties. The relaxivity of Gd(III) complexes is field dependent and, in the case the paramagnetic complex is part of a macromolecular system, it shows a maximum efficiency at ca. 1T. The theory of paramagnetic relaxation accounts well for this experimental observation as, at around 1T, provided that the exchange rate of the metal coordinated water is fast, there is a dominant effect of the long reorientational motion of the paramagnetic slowly moving systems. Currently, most of MRI scanners for small animals employ superconducting magnets that work at fields from 4.7 to 7 T (and even higher ones). High fields provide an overall increase of the signal intensity (SI) that allows the rapid acquisition of highly resolved images. However, in the presence of slowly moving Gd(III) loaded agents, the benefit on SI brought by the relaxation enhancement observed at low fields may well counterbalance the advantages offered by the high fields. This work aims at comparing “in vitro” and “in vivo” results obtained at 1T and 7T using as Gd(III) targeting agent the supramolecular adduct formed by amphiphilic Gd(III) complexes (Gd-AAZTAC17) incorporated into Low Density Lipoproteins (LDL) particles. The used amphiphilic Gd(III) complex corresponds to the Gd-AAZTA complex in which the exocyclic carbon has been replaced by a long -C<sub>17</sub> alkyl chain in order to pursue the incorporation in the lipidic core of LDL particles. In order to carry out the proposed comparison a newly available 1T scanner by Aspect (Aspect Magnet Technologies Ltd., Netanya, Israel) based on a NdFeB permanent magnet has been used.

**Methods.** The cellular uptake of the Gd-labeled LDL was first tested in vitro on HepG2 (human hepatoblastoma cancer cell line) and B16 (melanoma) tumor cells line. In vivo, Gd-labelled LDLs were administered to mice subcutaneously inoculated with B16 cells line. Magnetic Resonance Imaging (MRI) was performed at 1 (Aspect M2) and 7T (Bruker Avance 300) before, 5 and 24 hr post-contrast injection.

**Results.** Gd-loaded/LDL particles, used as imaging probes, were prepared following the already reported procedure. (1) Each LDL particle can be loaded with 250-300 Gd-AAZTAC17 molecules. Gd-AAZTAC17/LDL adduct displays a high relaxivity ( $r_{1p} = 20.4 \text{ mM}^{-1}\text{s}^{-1}$ ) at 1T (40 MHz) as witnessed by recording the  $1/T_1$  NMRD profile (Figure). Conversely, the relaxivity at 7T (300 MHz) is five times lower ( $r_{1p} = 4.0 \text{ mM}^{-1}\text{s}^{-1}$ ). Next, the 1T/7T comparison has been carried out on a tumor cell line (mouse melanoma B16-F10). LDL particles are avidly taken up by tumor cells that need their lipidic payload to form cellular and organelle membranes in their proliferative process. Cells have been incubated in the presence of Gd-AAZTAC17/LDL adduct (60  $\mu\text{g}/\text{ml}$ ) and after washing, have been transferred into glass capillaries for MRI analysis.  $T_1$ -weighted multislice spin echo images showed that % SI enhancement measured at 1T were significantly higher than at 7T. In particular, the capillary containing 5000 cells/ $\mu\text{l}$  was not significantly different from the control at 7T, whereas at 1T, it showed still a 30% enhancement over the control. As far as it concerns the “in vivo” evaluation, MRI was performed 5 hours after the injection of Gd-AAZTAC17 on C57 mice bearing transplanted melanoma tumor (B16), showed a significantly higher tumor signal intensity enhancement  $80 \pm 9 \%$  at 1T with respect 7T and  $30 \pm 13\%$  (Figure).



**Conclusions.** The herein reported results indicate that, for applications in which the paramagnetic agent is part of a slowly moving system a high-resolution 1T scanner yields a markedly higher contrast enhancement with respect to a high field one. Many molecular imaging applications can be properly carried out at this (low) field when using Gd(III)-based probes possessing long molecular correlation time. The availability of low cost, easy to use 1T MRI scanners may significantly widen the number of biological groups that should come to consider “in vivo” MRI as a complementary or alternative tool to other imaging modalities.

### References.

1) Geninatti Crich S, Lanzardo S, Alberti D, Belfiore S, Ciampa A, Giovenzana GB, Lovazzano C, Pagliarin R and Aime S, *Neoplasia*, 12, 2007, 1046 – 105