MR Imaging guided NCT by a dual Gd/B agent targeted to tumor cells via upregulated LDL transporters.

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Introduction. Boron Neutron capture therapy (BNCT) is a binary cancer treatment method that combines a cancer specific ^{10}B labeled drug and a neutron beam of a low energy sufficient for neutron capture to take place within the treated tissues[1]. These two therapeutic components are designed to be non-toxic themselves, while their combination results in a highly localized and lethal radiotoxic response at the cell level. Since, it has been estimated that ca. 10^9 ^{10}B atoms per tumor cell are needed to tackle an effective NC treatment of cancer, a non-invasive method able to quantify the boron concentration in the tumor and the surrounding tissues before irradiation with neutrons is necessary in order to improve and optimize the treatment. Thanks to its superb spatial resolution MRI appears to be the most appropriate technique to tackle this task using a suitable contrast agent. In fact, there is a direct proportionality between the observed relaxation enhancement and the concentration of the MRI reporter. Interestingly, a given cell can be visualized by MRI when the number of Gd^{3+} complexes is on the order of 10^8-10^9 per cell, i.e. a threshold close to that found for the number of ^{10}B atoms to provide an effective NCT treatment. The herein used probe[2] (Figure 1) is a conjugate containing a carborane unit (ten boron atoms), a Gd-complex as MRI reporter and an aliphatic (C15) chain for binding to Low Density Lipoproteins (LDL) particles to target tumor cells (B16 melanoma cells) through the high capacity LDL transporters that are up-regulated in many types of tumor cells. Furthermore, the combination of the boron and gadolinium compounds may be beneficial for enhancing the radiation dose to the tumor as ^{157}Gd (15% natural abundance) owns a very good cross-section for neutron capture.

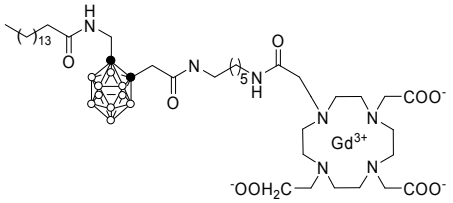

Figure 1

Methods. In vivo, Gd/B/LDLs were administered to mice subcutaneously inoculated with B16 cells. Tumor bearing mice received intravenously 0.1 mmol/kg of Gd-B-L/LDL. Fat-suppressed T1-weighted multislice spin-echo MR images were recorded before and 3, 6 and 24 hours after the contrast administration. Neutron irradiation was carried out inside the thermal column of the TRIGA-Mark II reactor at the University of Pavia, Italy.

Results and Discussion. Each LDL particle can load up to 150 imaging probes that correspond to 150 Gd and 1500 B atoms respectively. MRI tumor % Signal Intensity enhancements (SI) report about Gd and then Boron concentration and they were measured at the same time intervals for the tumor, healthy muscle, liver, spleen, kidneys. At 4h, the SI (and therefore the concentration of the Gd-containing probe) is ca. four-fold higher in the tumor than in the adjacent muscle tissues.(Figure) By measuring tissue R1obs and SI before and after Gd/B/LDLs administration, a ^{10}B concentration of 30±5 ppm was calculated in the tumor 4h after Gd-B-L/LDL administration, i.e. right above the established threshold required for BNCT treatment. Two groups of animals underwent the irradiation treatment one week after the subcutaneous injection of 1 million B16 cells at the bottom of the neck. A third group of non-irradiated mice was used as reference to assess tumor grown in the absence of any treatment. Whereas control groups showed an exponential growth of the tumor volume, in the Boron treated group tumor growth was significantly lower (Figure 2).

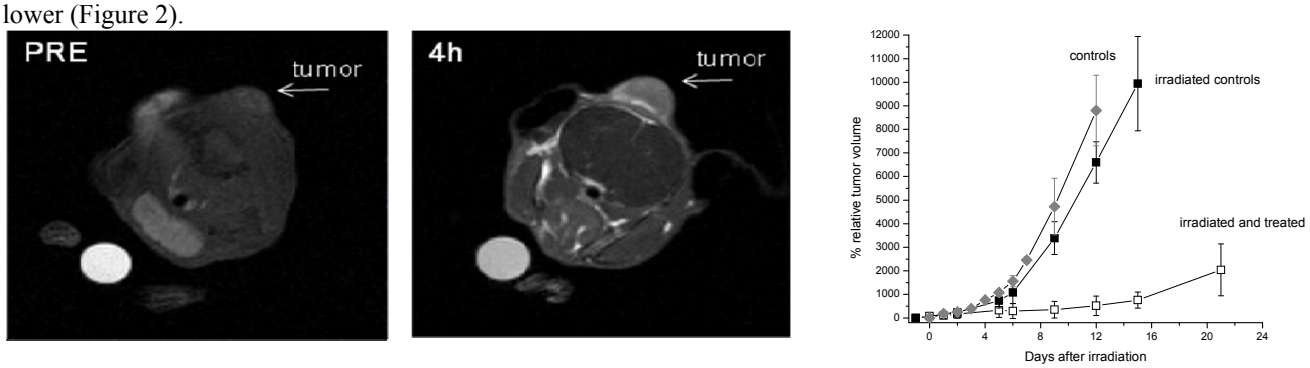

Figure 2

Conclusions. LDLs act as efficient and tumor selective carriers for the delivery of a new imaging probe containing Gd and Boron. It follows that imaging-guided BNCT appears possible as, from the signal enhancement generated by the paramagnetic Gd(III) complexes, we access to the key information that the ^{10}B concentration threshold has been reached.

References.

1) Barth RF et al, Clin. Cancer Res. 2005, 11, 3987-4002
2) Aime S et al, Org. Biomol. Chem, 2008, 6, 4460-4466.