MAGNETIC TARGETING OF MAGNEMITE NANOPARTICLES ENCAPSULATED INTO LIPOSOMES: AN IN VIVO STUDY IN MICE TUMORS MONITORED BY MRI

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Objectives. Nanoparticles of maghemite are excellent contrast agent for MRI of the reticulo endothelial system [1]. Their internalization into liposomes [2] (magnetoliposomes, see Fig. 1) allows to target tumors thanks to two classical mechanisms: passive targeting with the PEG surface and active targeting using specific ligands. The aim of this study was to explore a third targeting mechanism, using the magnetic properties of the magnetoliposome submitted to an external magnetic field.

1. Materiels and methods. Magnetoliposomes were synthesized (UMR 8612) by ionic ferrofluids (UMR 7612) and PEG-lipids, then their physicochemical characteristics and relaxivities were determined. The *in vivo* displacement of magnetoliposome under calibrated magnetic field was measured under light microscopy, in order to estimate the velocity induced by the applied magnetic force. *In vivo*, swiss nude male mice bearing a PC3 tumor in each flank (prostate adenocarcinoma) received an IV injection of magnetoliposome after a small magnet was fixed above the skin in front of one tumor (0,3 T and 11 T/m). A total of 38 animals was imaged with MRI, using different sequences. Influence of several

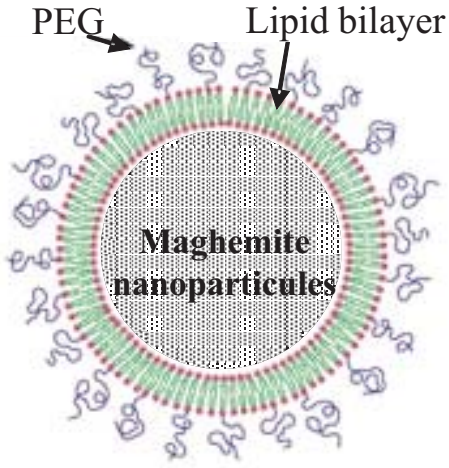

Fig. 1. PEG-Magnetoliposome.

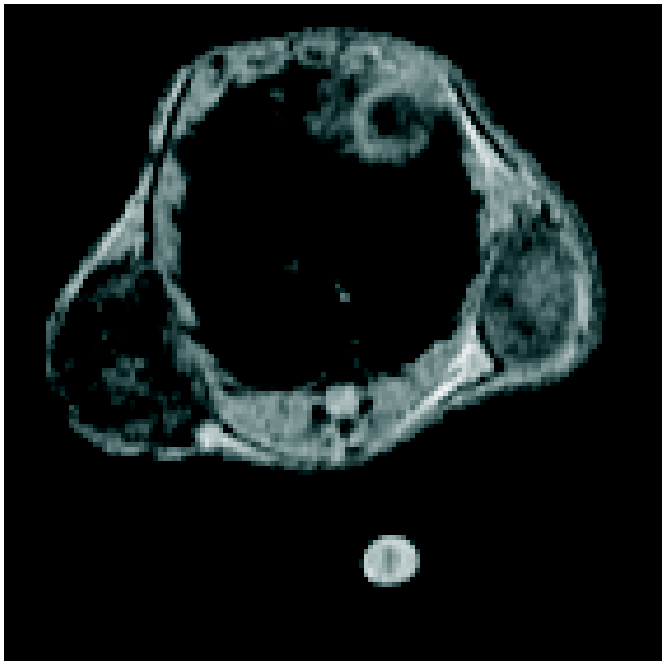

Fig. 2. MRImaging of a mouse with a subcutaneously implanted tumor in each flank. The preferential accumulation of magnetoliposome in tumor exposed to a magnetic field, induce a lower signal.

parameters were evaluated: MRI sequence sensibility, injected dose and duration of the field application. The signal intensity was measured on each animal and normalized by the signal of an oil phantom (SI). Then, enhancement toward the control group (SI_{ref}) was computed: $ENH(\%) = (SI - SI_{ref})/ SI_{ref}$. An histological analysis of the tumors, liver and spleen was then performed.

Results. The order of magnitude of the velocity obtained was 20 μm/s under a magnetic field of 0.13 T with a gradient of 25 T/m. *In vivo*, the tumour under the magnet experiences a strong heterogeneous negative enhancement (see Fig. 2), down to –52%, as compared to –7% for the opposite tumour (with the 3D-SPGR sequence). The most sensitive sequences were gradient echo ones. Maximum enhancement was obtained after 3 h magnet application. Histologically, an intra capillary accumulation of clusters of magnetoliposomes was observed at 24 h, only in tumour with magnet.

Conclusion. This study confirms the feasibility of magnetic targeting of stealth magnetoliposomes, with an iron dose of 5 to 15 mg Fe/kg and a duration of magnet application of 1 to 24 h. Additional histological studies are necessary to understand the exact accumulation mechanism. This original targeting to tumours could be used to deliver therapeutic substances to tumours [2] or to perform a therapeutic hyperthermia [3].

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