Exploring the tumour extracellular matrix by in vivo Fast Field Cycling Relaxometry after the administration of a Gadolinium based MRI contrast agent

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^{1}H Fast-Field Cycling NMR relaxometry is proposed as a powerful method to investigate tumour stroma *in vivo* by the administration of a Gd based contrast agent. Since the extracellular microenvironment of a tumor can affect the growth and progression of the tumor as well as the development of metastatic disease, it is essential to better understand the interplay between the tumor and its surroundings [1]. To perform this study, prototype FFC-NMR equipment with a wide bore magnet was used for the acquisition of Nuclear Magnetic Resonance Dispersion (NMRD) profiles on animal models [2]. Mouse mammary adenocarcinoma cells, namely TS/A and 4T1, were injected in the muscle of the hind-limb to obtain tumour xenografts. The two cell lines were selected because they display different aggressiveness and metastatic potential (i.e. TS/A<4T1) [3]. When tumour mass cover more than 65% of the leg, NMRD profiles were acquired pre- and post-injection of ProHance (e.g. Gd-HPDO3A, Bracco Imaging S.p.A., Milan, Italy) (Figure 1).

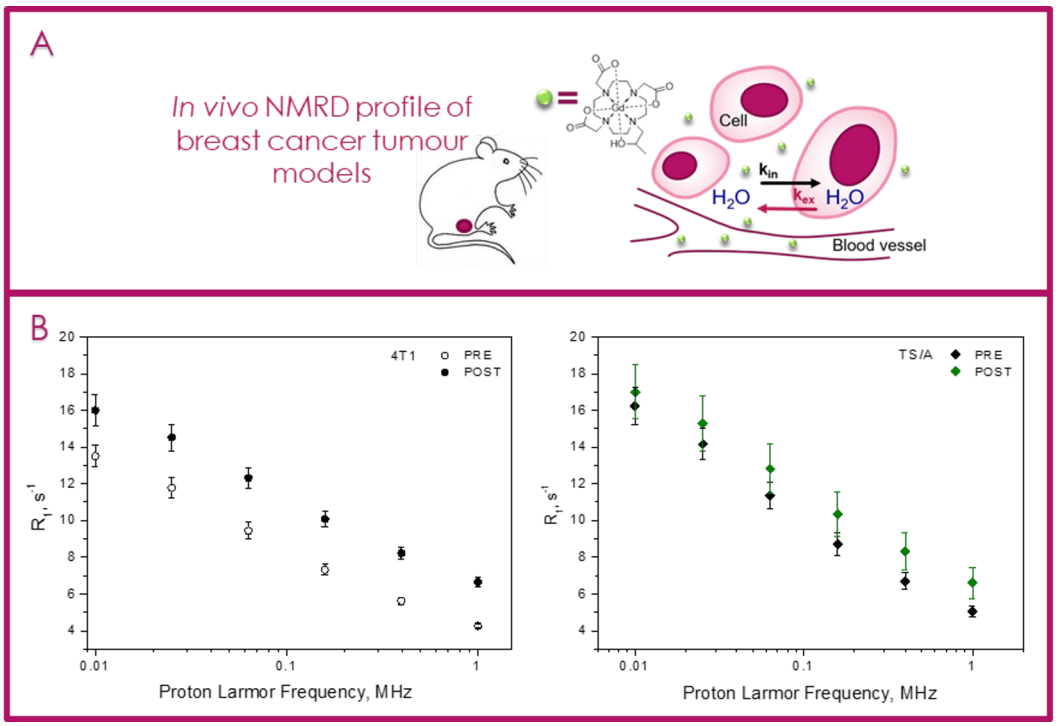

Figure 1. A) Schematic representation showing the extracellular distribution of ProHance (green circle) in the tissue, after the injection in a tumour bearing mouse model. Water molecules reside inside the cells (V_{in} and R_{1in}) and in the extracellular space (V_{ex} and R_{1ex}). B) NMRD profile of tumour bearing (4T1 on the left and TS/A on the right) mouse leg before and after the injection of ProHance.

At magnetic field strengths < of ca. 1 MHz the differences in the relaxation rates of the intra- and extra-cellular compartment (V_{in} and V_{ex}, respectively) become of the same order of magnitude of the exchange rate across the cellular membranes. Under this condition, the water exchange rate between the two compartments yields to a biexponential magnetization recovery that can be analysed by fitting the experimental data with the two-Site eXchange (2SX) model [4]. Using this model it was possible to extrapolate for the two compartments both relaxation properties and water kinetic constants for water exchange across cell membranes. The method allowed us to determine the effect of the "matrix" on the water proton relaxation times and, in turn, to get some insights of the composition of this compartment, till now, largely unknown.

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