

Extracellular sodium MRI, a non-invasive endogenous marker for tumoral response to photodynamic therapy associated with nitroglycerin.

Carole D. Thomas^{1,2}, Florent Poyer^{1,2}, Philippe Maillard^{1,3}, Mihaela Lupu^{1,2}, and Joel Mispelter^{1,2}

¹Institut Curie, Orsay, France, ²INSERM U759, Orsay, France, ³CNRS UMR176, Orsay, France

The aim of the study was to assess by sodium and proton magnetic resonance imaging (²³Na/¹H MRI) the efficacy of a treatment protocol that combines photodynamic therapy (PDT) and nitroglycerin (NG) on human retinoblastoma tumors xenografted on nude mice. We have chosen specifically the least responsive tumoral line to this treatment. Sodium MRI becomes an interesting imaging modality due primarily on the intrinsic sodium concentration gradient between intra (<10 mM Na) and extra (150mM Na) cellular compartments and secondly on higher magnetic field availability of MRI scanners used in clinical environment [1,2]. PDT uses a non-mutagen photosensitizing agent activated by visible light (glicoconjugated-meso-substituted-porphyrin derivative). Absorption of light initiates the photochemical reactions leading to the generation of cytotoxic products. These are responsible for cellular death during the light activation. NG is known generally to relax blood vessels and to increase blood flow [3].

Imaging: ¹H and ²³Na MRI were performed at 4.7 T using a Bruker Biospec small animal MRI scanner. The MRI probehead consists of a double tuned volume resonator (birdcage) used for transmitting / receiving ¹H signals and transmitter ²³Na r.f. channel, and a surface coil nested inside the birdcage for receiving ²³Na signals. Multi-slice, multi-echo ¹H images (respiratory trigger, FOV=6.8cm, TE=12ms, NE=10, matrix 256x256, slice thickness 1mm) were recorded for localization purposes, and tumor volume determination. Single-slice, multi-echo ²³Na images (NE=28, respiratory trigger, TE=6.7ms, FOV=6.8cm, matrix 64x64, slice thickness 3mm) were recorded to image mainly the extracellular tumor compartment. The sodium resolution was (1x1x3) mm³ and the acquisition time was about 75 min (160 averages).

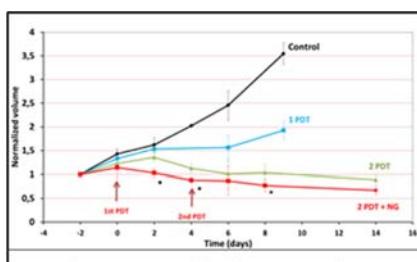


Fig. 1: Normalized tumor volume evolution of Retinoblastoma

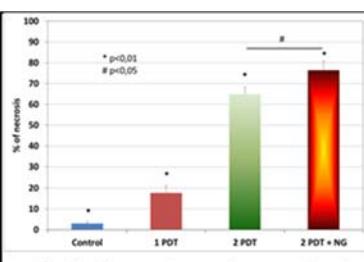


Fig. 2 : Percentage of necrosis at the end of the follow-up

Treatment protocol: Human retinoblastomas were subcutaneously xenografted on the flank of nude mice. Three regimens were devised for this study: control, one PDT treatment without NG ointment and two PDT treatments (at four day interval) with and without NG ointment (0.2mg) application 1h before treatment.

Results: The follow-up was performed during 14 days. One PDT treatment did not stop the tumoral progression, two PDT stopped it and NG application increase the % of necrosis (Fig.1-2). The NG potentiates the PDT treatment probably by increasing the PS concentration in the tumor. Local intensity increase in sodium

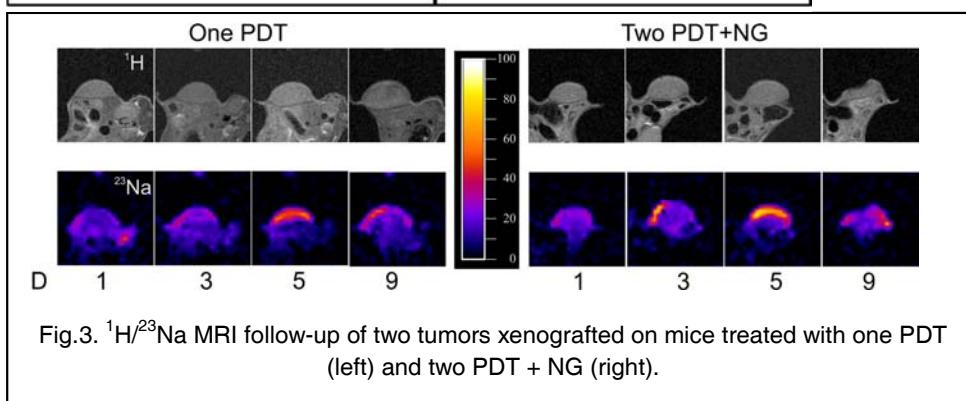


Fig.3. ¹H/²³Na MRI follow-up of two tumors xenografted on mice treated with one PDT (left) and two PDT + NG (right).

treatment.

contrast implies a cellular destruction and hence an increase of extracellular volume (Fig.3). ²³Na MRI directly monitors rapid variations of local sodium concentrations in a non-invasive way; it can be used to follow-up the tumor response to therapy and more to change the treatment protocol in function of the tumor response [2].

Conclusion: Our work indicates that *in vivo* dual ¹H and ²³Na MRI is a non-invasive technique well suited for both longitudinal follow-up and early treatment assessment. Furthermore, the association of NG ointment with PDT increases the treatment efficiency for the less responsive tumoral line to this

References: [1] Thomas CD et al., Proc. Int. Soc. Mag. Reson. Med., 2008, 16: 2795. [2] Lupu M et al., PDPDT, 2009, 6: 214-220. [3] Maruhashi et al., Arterioscler Thromb Vasc Biol, 2013, 33, 1401-1408.