In vitro and *in vivo* evaluation of GdDO3NI as a hypoxia targeting MRI T_1 contrast agent

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Introduction:

Heterogeneously distributed hypoxic cores in tumors are known to affect radiation sensitivity and promote development of metastases [1], therefore the ability to image the tumor microenvironment *in vivo* will provide useful prognostic information. Noninvasive imaging based methods such as MRI are particularly suitable for longitudinal measurements and generation of three-dimensional spatial maps of tumor hypoxia [2]. Previous research demonstrated that 2-nitroimidazole accumulated in hypoxic tissues due to an enzyme mediated reduction of the nitro group in hypoxic conditions [3]. Here we report the *in vitro* and *in vivo* evaluation of GdDOTA monoamide conjugate of 2-nitroimidazole, GdDO3NI (Fig 1b), as a novel hypoxia targeting MRI T_1 contrast agent.

Materials and Methods:

GdDO3ABA (Fig 1a) was used as a control agent and GdDO3NI as hypoxia targeting agent. *In vitro* measurement of T_1 relaxivity (r_1) of these agents was performed at 37°C using a serial dilution saline phantom. The concentrations used for the measurements were in the range 0-4 mM. For the r_1 measurements, a spin-echo sequence was employed with several TR values (0.1-6s). Relaxivity was extracted as slope of linear fit to relaxation rates (R_1) vs. concentration. For *in vivo* studies, 10 Copenhagen rats were implanted subcutaneously with syngeneic AT1 prostate tumors. Imaging studies were performed when the tumor sizes reached ~3cc. T_1-weighted images (TR/TE = 200/10 ms, FOV= 5 cmX5 cm, matrix=128X128, slice thk= 1 mm) were obtained pre and post injection of 0.1 mmole/kg body wt contrast agent (GdDO3ABA or GdDO3NI, n= 5 each). Images were acquired every 30 seconds during basline and upto 3 minutes post injection followed by acquisition every minute up to 15 minutes and then once every 10 minutes up to 150 min post injection. Data analysis was performed by segmenting the voxels in the tumor region based on a criterion of 50% enhancement at 90 s post injection.

Results and Discussion:

A linear fit to the relaxation rates (R_1) vs. concentration data (Fig 2) yielded the relaxivity value of 4.74 ± 0.03 mM^{-1} s^{-1} and 5.21 ± 0.04 mM^{-1} s^{-1} for GdDO3ABA and GdDO3NI, respectively. Contrast agent kinetics were compared following intravenous injections of GdDO3NI and GdDO3ABA in AT1 rat prostate tumor bearing animals. Qualitatively, the time course signal intensities showed a clear difference in the enhancement patterns for the two agents (GdDO3ABA and GdDO3NI) and between well perfused and poorly perfused regions (Fig 3). In case of GdDO3NI, a statistically significant difference in the contrast enhancement was observed between well perfused (and consequently well oxygenated) regions and poorly perfused (and potentially hypoxic) regions at late time points (60-150 min) where as for GdDO3ABA, no statistically significant difference between the regions was observed at late time points. Our results suggest that GdDO3NI can be used as a hypoxia targeting MR contrast agent.

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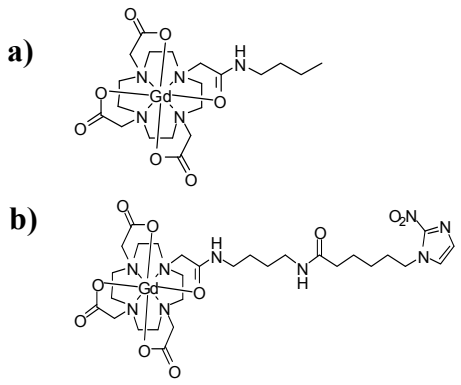

Figure 1: *Structure of a) GdDO3ABA and b) GdDO3NI.*

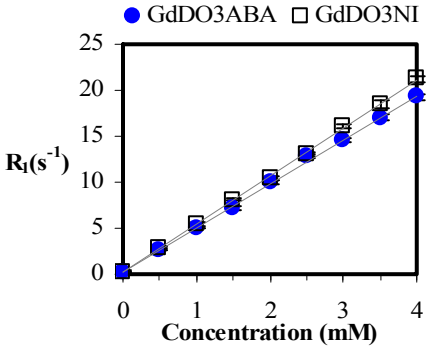

Figure 2: *Graph of R_1 vs. concentration for the compounds GdDO3ABA (●) and GdDO3NI (□).*

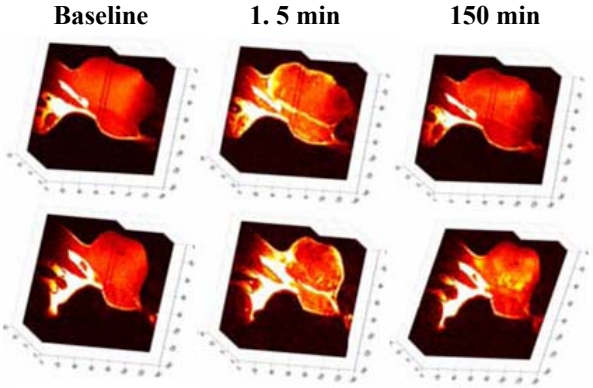

Figure 3: *T_1wt 3D stacks (displayed on a common scale) following injection of 0.1mmole/kg body wt GdDO3ABA (top row-control) and GdDO3NI (bottom row) at pre injection, 1.5 min and 150 min post injection.*

References:

1. Int J Radiat Biol 2006;82(10):699-757.
2. Neoplasia 2009; 11(3): 247-259.
3. J Nucl Med 2008;49 Suppl 2:129S-148S.