Molecular imaging beyond contrast generation: Utility of BIRDS

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INTRODUCTION:

Conventional T_1 and T_2 contrast agents (e.g., Magnevist and Molday Ion) offer images without reporting on local environment of tumor. A particular challenge for diagnosis and treatment of cancer is the need for non-invasive imaging methods that would allow quantitative identification of tumor status prior to, during, and after therapy. Our motivation is to go beyond the shades of gray in typical molecular/cellular MRI and follow the chemical and physiological status of the contrasted tissue as a function of disease progression and treatment. A new ultra-high speed 3D chemical shift imaging (CSI) method, called **b**iosensor **i**maging of **r**edundant **d**eviation in **s**hifts (BIRDS) is key [1], which requires that we detect protons emanating from the contrast agent (e.g., $TmDOTP^{5-}$), itself instead of the agent's effect on water proton relaxation times. BIRDS can be used for temperature and pH mapping in vivo [2] and also allow quantitative **c**hemical **e**xchange **s**aturation **t**ransfer (CEST) contrast [3]. Here we tested if BIRDS could also be useful for molecular reporting in the presence of strong T_1 and T_2 contrast agents typically used in molecular/cellular MRI experiments. We expect that combination of agents like $TmDOTP^{5-}$ and Magnevist or Molday Ion may improve the ability of molecular imaging with MRI. As a prelude to that goal, here we investigated how the sensitivity and resiliency of the $TmDOTP^{5-}$ proton signals is affected by the addition of Magnevist, Molday Ion, and by liposomal encapsulation. Encapsulation in liposome allows for local signal enhancement in addition to the traditional advantages offered by liposomes.

METHODS:

$TmDOTP^{5-}$ was mixed with Magnevist and with Molday Ion and their pH adjusted to desired values between pH 6.5-8. Encapsulation in liposome was accomplished by thin film hydration of DPPC with $TmDOTP^{5-}$ solution at 55 °C for 1 hour followed by five freeze-thaw cycles and resulting liposomal suspension dialyzed. ^1H spectra were obtained using a 500 MHz Bruker spectrometer. Phantom images were obtained on a 9.4 T Varian horizontal bore spectrometer using a surface coil RF probe.

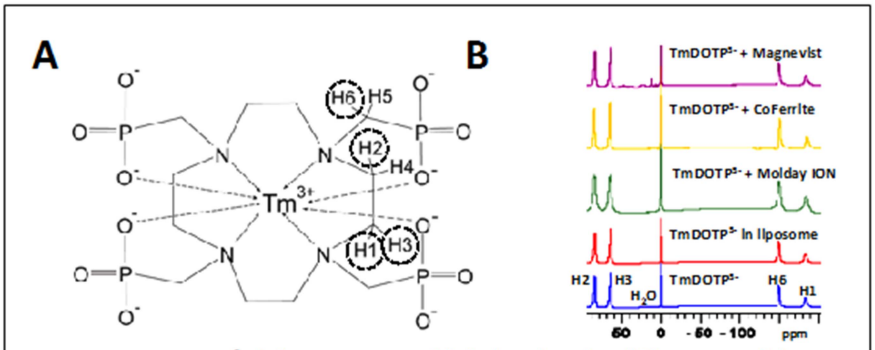

Figure 1. $TmDOTP^{5-}$ (A) structure and (B) signal under different conditions.

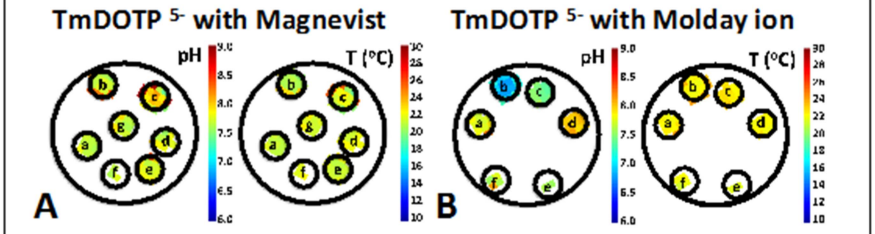

Figure 2. pH and T mapping with (A) Magnevist and (B) Molday ion in vitro.

RESULTS and DISCUSSION:

Fig. 1 and Tab. 1 show how resilient the $TmDOTP^{5-}$ signals are in different environments. The ^1H spectra of $TmDOTP^{5-}$ in Fig. 1 show that the signals remain unaffected by presence of Magnevist, Molday Ion, and even when $TmDOTP^{5-}$ is encapsulated in liposomes where ~80% encapsulation efficiency was achieved with BIRDS amplification of up to 500 times in liposomes. Temperature (T) and pH sensitivities in Tab. 1, which are represented in terms of °C per ppm and pH units per ppm respectively, are within 10% of sensitivities for pure $TmDOTP^{5-}$ [1]. Fig. 2 shows the resiliency of $TmDOTP^{5-}$ in an imaging format. Fig. 2A shows $TmDOTP^{5-}$ in 1:5 ratio with Magnevist, where all samples had the same pH of 7.5, sample c had the lowest $TmDOTP^{5-}$ concentration (of 0.5 mM), sample f was $TmDOTP^{5-}$ itself (2 mM), and sample g was 6.25 mM $TmDOTP^{5-}$ in liposome. Fig. 2B shows $TmDOTP^{5-}$ in 1:10 ratio with 0.05 mg of Fe/ml of Molday Ion (e.g., 0.05 mg Fe/ml in 5 mM $TmDOTP^{5-}$), where all samples had different pH values and sample e had the lowest $TmDOTP^{5-}$ concentration (of 1.25 mM). The comparison shows uniform pH and T in Fig. 2A and variable pH and uniform T in Fig. 2B, which are all within independently verified measurements. The only situation where $TmDOTP^{5-}$ signals were compromised is when concentrations were low. These results lend confidence to use agents like $TmDOTP^{5-}$ in conjunction with various other contrast or encapsulating agents for MRI contrast.

Table 1	+ Magnevist		+ Molday Ion		in liposome	
	T	pH	T	pH	T	pH
H1	+1.1	-4.2	+1.1	-4.2	+1.2	-4.1
H2	-0.6	+4.2	-0.6	+3.8	-0.6	+3.9
H3	-0.5	+3.6	-0.4	+3.3	-0.4	+3.4
H6	+1.0	-3.9	+1.0	-3.8	+1.0	-3.9

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