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is used as a model drug and the release behaviors have been monitored *in vitro*. Results show that variation of magnetic field ends with distinct release rate and larger particles enhance release rate more than the smaller counterparts. To conclude, an injectable PF127 ferrogel with tunable release rate has been developed for loading and delivering hydrophobic drugs. Stability, biodistribution and toxicity of the ferrogel under physiological environment are currently under investigation.

**J079**

**NEW SUITABLE BIMODAL CONTRAST AGENTS FOR MRI AND OPTICAL IMAGING**

Sophie Laurent<sup>1</sup>, Luce Vander Elst<sup>1</sup>, Chantal Galaup<sup>2</sup>, Claude Picard<sup>2</sup>, Robert N. Muller<sup>1</sup>

<sup>1</sup>NMR and Molecular Imaging Laboratory, University of Mons, Mons, Belgium, <sup>2</sup>Laboratoire SPCMIB, Univeristé Paul Sabatier, Toulouse, France.

Three Gd- and Tb-PMN-tetracetate derivatives 1–3 (PMN = [2,6-pyridinediylbis (methylenenitrilo)] tetraacetic acid, respectively R = H (1), COO- (2), CONHCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>COpeptide(3)) are synthesized and evaluated for a potential use as bimodal contrast agents for MRI and optical imaging (figure 1). The peptide complexes 3 (TLVSSL) was selected to target apoptotic cells. Gd-complex: O-17 chemical shift analysis shows the presence of 2 coordinated water molecules. The proton relaxivity is increased as compared to Magnevist

or Omniscan as a result of the presence of 2 water molecules in the first coordination sphere (figure 1). The water residence time is short (32–42 ns at 310 K) and close to the optimal value. The possible interaction of the complex with serum albumin was tested. No binding of the Gd-complex to HSA could be detected. The stability was first tested in a phosphate buffer (pH=7). No significant change of the relaxivity was observed. The possible transmetallation process was then assessed by the measurement of the evolution of the proton longitudinal paramagnetic relaxation rate (R1P) of a phosphate buffer containing an equimolar amount of Gd-complex and Zn ions (2.5 mM). The stability versus Zn(II) ions is comparable (complex 1) or higher (complexes 2 and 3) to that of Gd-DTPA-BMA. Tb-complex: The comparison of the luminescence data in heavy and hydrogenated water confirms the presence of two water molecules in the first coordination sphere of the complexes. Experiments in phosphate buffer and in presence of bidentate coordinating anions (citrate, carbonate, bicarbonate) showed the kinetic inertness of the Tb-complexes. The values of the quantum yield obtained upon ligand excitation were determined to be 8.5, 10 and 4% for complexes 1, 2 and 3 respectively. The Φ<sub>tot</sub> value is within the actual range of commercially available di-aquo Tb complexes. The Gd and Tb complexes show interesting properties either for MRI or for optical imaging: for the Gd-complex, a high proton relaxivity and an acceptable stability in physiological medium; for the Tb-complex, energy transfer from pyridine to terbium and a long luminescence lifetime to avoid the overlap with biological background. The first tests on apoptotic cells with Gd-PMN peptide are very promising.

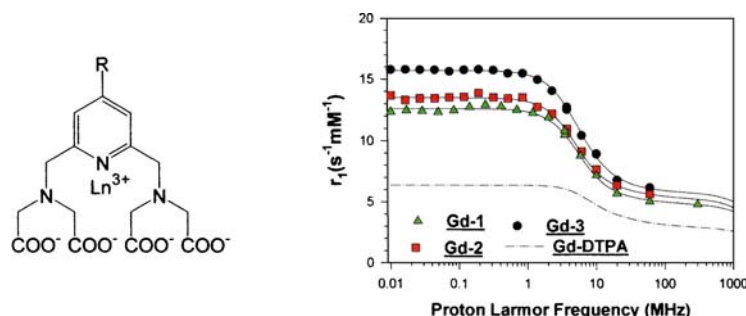


Figure 1 : Structures of Ln-PMN derivatives and NMRD profiles of their Gd-complexes

**J080**

**COMPARISON OF GADOLINIUM LOADED AND EMPTY CARBON NANOTUBES AS HIGH PERFORMANCE MRI CONTRAST AGENT**

Annie M. Tang<sup>1,3</sup>, Kelvin Wong<sup>1,2</sup>, Jeyarama S. Ananta<sup>4</sup>, Edmund Y. Lam<sup>3</sup>, Lon J. Wilson<sup>4</sup>, Stephen T. Wong<sup>1,2</sup>

<sup>1</sup>Center for Biotechnology and Informatics, The Methodist Hospital Research Institute, Houston, TX, USA, <sup>2</sup>Department of Radiology, The Methodist Hospital Research Institute and Weill Cornell Medical College, New York, NY, USA, <sup>3</sup>Department of Electrical and Electronic Engineering, The University of Hong Kong, Hong Kong, China, <sup>4</sup>Department of Chemistry, Rice University, Houston, TX, USA.

Introduction: Gadolinium loaded ultra-short single walled carbon nanotubes (US-tubes) has been proposed as an effective high r<sub>2</sub> relaxivity contrast agent for use in MR molecular imaging. However, the true active ingredients for inheriting its high performance r<sub>2</sub> characteristics, is remain unknown. In this study, we compare the R<sub>2</sub> and R<sub>2</sub>\* relaxation rate of the US-tubes with/without Gadolinium ions encapsulation. Methods: Two types of US-tubes MRI phantoms were prepared: (i) Gadonanotubes with 41 μM Gd and (ii) empty US-tubes. Each type of nanotubes was

dispersed in pluronic solution with carbon concentration of 275 mg/L and transferred to a 1 cc syringe for MRI imaging. MRI imaging was performed in a 3T MRI scanner using a 35 mm volume coil with 2D spin echo (TR=1500 ms, TE=20–80 ms with 10 ms increment) and 2D gradient echo (alpha=90, TR=1500 ms, TE=20–80 ms with 5 ms increment) sequences to evaluate the R<sub>2</sub> and R<sub>2</sub>\* respectively. A 1 mm thick single slice was obtained at each TE cutting in the middle of the 3.5 cm long filled syringe placed parallel to the main magnetic field. T<sub>2</sub> and T<sub>2</sub>\* were determined by linear fitting of the measured image intensities at each TE at each phantom into log(S) = log(S<sub>0</sub>)-TE/T<sub>2</sub> and log(S) = log(S<sub>0</sub>)-TE/T<sub>2</sub>\*. Results and Discussions: Table 1 shows the estimated R<sub>2</sub> and R<sub>2</sub>\* relaxation rates of the phantoms. R<sup>2</sup> represents the coefficient of determinations of the linear fitting. Both Gadonanotubes and empty US-tubes show high R<sub>2</sub> and R<sub>2</sub>\* relaxation rates with the R<sub>2</sub>\* being 6–11% stronger than R<sub>2</sub>. The slight increase in R<sub>2</sub>\* may attribute to bulk magnetic susceptibility effects due to the presence of metal ions inside the US-tubes. Nethertheless, the R<sub>2</sub>\* observed is small when compared with that of other superparamagnetic contrast agents which usually show a few times increase in R<sub>2</sub>\*. This may be due to the low concentration (in μM) and lose density packing of the metal ions inside the tubes. For empty US-tubes, it is observed that its relaxivities are as good as Gadolinium loaded US-tubes. Additional Gd<sup>3+</sup> loading does not

significantly increase the relaxivities of the US-tubes. Therefore, it is reasonable to consider using empty US-tubes as a high performance MRI

contrast agent as well as drug/gene delivery carrier, with the delivery items being encapsulating inside its hollow interior space.

	Gadonanotubes	Empty US-tubes
$R_2 (s^{-1})$	26.76 [ $R^2=0.99$ ]	23.67 [ $R^2=0.99$ ]
$R_2^* (s^{-1})$	29.72 [ $R^2=0.99$ ]	25.23 [ $R^2=0.99$ ]

Table 1

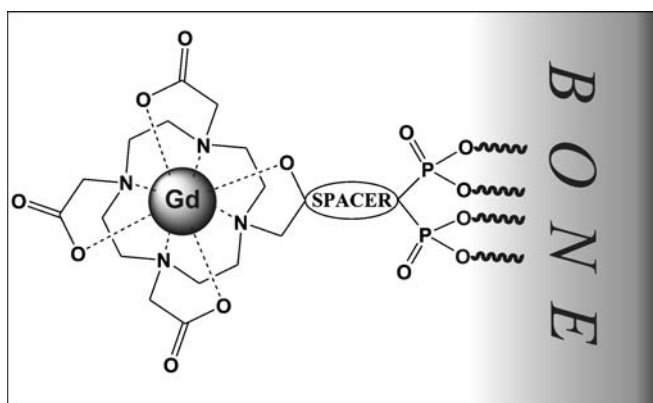
## J081

### DOTA-LIKE COMPLEXES BEARING A BISPHOSPHONATE MOIETY—BONE-SEEKING AND ION-SENSING AGENTS

Vojtech Kubicek, Ivan Lukeš

Department of Inorganic Chemistry, Charles University in Prague, Faculty of Science, Prague 2, Czech Republic.

Three bone-targeting metal carriers for applications in molecular imaging have been prepared. DOTA-like core was used as a metal chelating group. The chelator was attached to a bisphosphonate moiety that is known to adsorb efficiently on bone tissue. The compounds form stable DOTA-like complexes with Ln(III) ions. The bisphosphonate group is not coordinated. An *in vitro* study was performed using  $^{159}\text{Tb}$  complexes as reporters and an aqueous suspension of hydroxyapatite as a model of bone tissue. The results have shown a strong and swift adsorption of the complexes on hydroxyapatite. *In vivo* SPECT/CT experiments using  $^{177}\text{Lu}$  have shown a significant uptake and a long retention of the complexes in joints and on bone surface of Lewis rat. Studied Gd(III) complexes exhibit MRI properties that are common for low-molecular compounds with one water molecule coordinated to the metal ion. Relaxivity (MRI efficiency) of the complexes is increased by presence of the rich second hydration sphere. Further, upon adsorption on the surface of hydroxyapatite, relaxivity was significantly improved. In addition, the complexes interact with divalent metal ions. The interaction of Gd(III) complexes results in a formation of polymeric bisphosphonate complexes and consequently in an increase (300–500%) of relaxivity. In the field of MRI contrast agents, this is the highest response on presence of metal ions ever reported. On basis of the results, it could be concluded, that the studied compounds are promising bone-targeting (MRI, PET, SPECT) and metal-ion-responsive (MRI) contrast agents.



## J082

### SPECIFIC DELIVERY AND RELEASE OF CYTOTOXIC Gd3+ IONS TO TUMOR CELLS THROUGH VITAMIN B12 BIOCONJUGATES

Eliana Gianolio<sup>1</sup>, Patrizia Siega<sup>2</sup>, Jochen Wuerges<sup>2</sup>, Francesca Arena<sup>1</sup>, Silvano Geremia<sup>2</sup>, Silvio Aime<sup>1</sup>, Lucio Randaccio<sup>2</sup>

<sup>1</sup>Chemistry IFM, University of Torino, Torino, Italy, <sup>2</sup>Chemical Science, University of Trieste, Trieste, Italy.

Mammalian cells require Vitamin B12 as enzyme cofactor. Mammals have developed a specific internalization pathway for this essential micronutrient, and fast proliferating cell types require even higher amounts of it. This observation has given considerable potential to the use of vitamin B12 analogues as imaging and therapeutic agents. In this poster we describe the synthesis and applications of a VitB12-Gd-DTPA derivative to specifically deliver and release cytotoxic Gd<sup>3+</sup> ions to tumor cells. Two new bioconjugates of vitamin B12 resulting from the esterification of the ribose 5'-hydroxyl of VitB12 with the metal-chelating agents DTPA or TTHA have been synthesized and characterized. The major difference between the two systems is the denticity of the ligands, that results in significant differences in the ability to release Gd<sup>3+</sup> ions to cells and in different hydrolysis rates of the ester linkage between VitB12 and the ligand. Hydrolysis rate constants of  $4.1 \times 10^{-3} \text{ min}^{-1}$  and  $4.9 \times 10^{-4} \text{ min}^{-1}$  and  $t_{1/2}$  values of 175 min and 1414 min have been determined for 1 and 2, respectively. As far cell labelling concerns, whereas 1 showed an increased uptake in K562 cells, internalization of 2 was negligible at all the investigated concentrations. It has been demonstrated that, in the case of 1, the internalization process involves free Gd<sup>3+</sup> ions and that the presence of the VitB12 moiety is crucial in the cell recognition process. Viability tests showed that in the presence of 1 the cell viability is markedly reduced while the effect of 2 is negligible. One can surmise that the involvement of the ester oxygen atom in Gd-coordination in 1 is responsible for its lower stability towards hydrolysis and in its higher ability to release Gd<sup>3+</sup> ions at the binding sites on the cellular membrane. The high toxicity observed for K562 cells treated with 1 appears as a further indication of the massive uptake of Gd<sup>3+</sup> ions.

