A single amino acid Gd-complex as a modular tool for high relaxivity MR contrast agent development.

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Target audience: Gd-based T1 agent development for high fields, basic science studies, chemistry.

Purpose: Magnetic resonance imaging (MRI) at high magnetic fields benefits from an increased signal to noise ratio, however T_1 based MR contrast agents show decreasing relaxivity (r_1) at higher fields. It was our aim to design new Gd-based contrast agents that allow us to control the rotational dynamics (τ_R) of the molecule while maintaining a rapid mean water residency time ($_M$). Control over these parameters should allow the synthesis of high field, high relaxivity contrast agents.[1]

Methods: We investigated applications of the alanine analogue of Gd(DOTA), Gd(DOTAla). Fmoc protected DOTAla suitable for solid phase peptide synthesis was synthesized and integrated into polypeptide structures containing 1-3 Gd(DOTAla) complexes (Gd**L1,** Gd_2**L2,** Gd_3**L3**). Water exchange kinetics for the inner-sphere water ligand were determined by measurement of the temperature dependence of the transverse relaxation time T_2 of $H_2{}^{17}O$ in the presence and absence of Gd**L1**. Relaxivities were determined through measurement of T_1 using inversion recovery at different field strengths ranging from 0.47 T to 11.7T. To address kinetic inertness, we measured the full transchelation of Gd(III) from the complexes Gd**L1**, Gd_2**L2** Gd_3**L3** to a DTPA derivative with higher thermodynamic stability at pH 3 and 37 °C.

Results: The mean water residency time at 37 °C was found to be optimal (τ_M = 17 ± 2 ns) for relaxivity. The facile integration of the DOTAla into polypeptide structures allowed investigation of a variety of multimeric structures. Relaxivity was determined for 6 new compounds along with FDA-approved agents gadofosveset and gadoteridol at 5 magnetic fields (0.47 – 11.7T). The trimers performed best at all fields: r_1 = 12.9 mM^{-1} s^{-1} per Gd for Gd_3**L3** at 1.4T, 37 °C. T_1 measurements indicated that Gd_3**L3** shows greater relaxivity at low, intermediate and high fields than the clinically used small molecule contrast agent gadoteridol while also outperforming gadofosveset/HSA at intermediate and high fields (Figure 1).

Discussion and Conclusion: Gd_3**L3** is superior to commercial contrast agents gadoteridol and gadofosveset /HSA (human serum albumin) at high fields. The modularity of design, the ease of solid phase synthesis, high kinetic inertness ($t_{1/2}$ = 61±4h) for Gd_3**L3**), and optimal water exchange rate renders the Gd(DOTAla) scaffold a suitable platform for the development of high field T_1 agents based on Gd**.**

References: (1) Caravan, P. et al, (2009) Influence of molecular parameters and increasing magnetic field strength on relaxivity of gadolinium- and manganese-based T1 contrast agents. *Contrast Media Mol. Imaging,* **4**, 89–100.

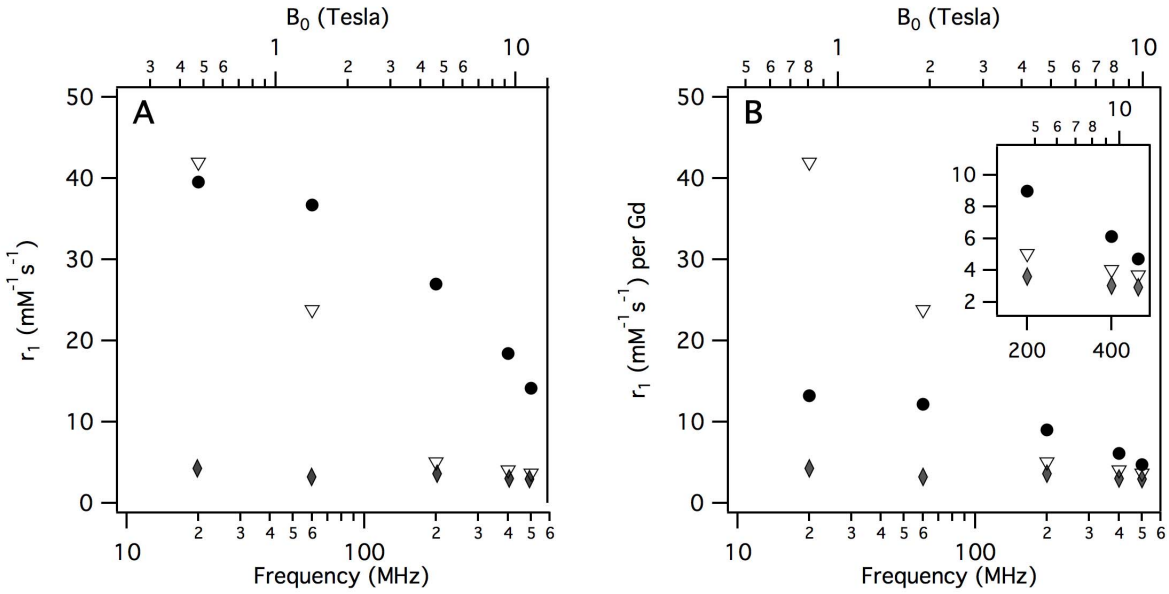

Figure. Relaxivities of Gd_3**L3**(●), gadofosveset with excess HSA (▽) and gadoteridol (♦) as a function of magnetic field at 37 °C. (A) Relaxivity plotted per [molecule] showing that Gd_3L3 with its intermediate correlation time is a much more potent relaxation agent that slow (gadofosveset/HSA) or fast (gadoteridol) tumbling compounds at1.41T and higher frequencies. (B) Relaxivity plotted per [Gd] shows that the intermediate correlation time of Gd_3L3 results in higher relaxivities at high fields.