Radical Dendrimer-Based MRI Contrast Agents: In Vivo Applications and Studies on Influencing Relaxivity Factors

José Vidal-Gancedo[1,2], **Vega Lloveras,**[1,2] Yufei Wu,[1] Ehsan Shirdel,[1] Songbai Zhang,[1] Silvia Lope,[3] Ana Paula Candiota[2,4,5]

[1]Institut de Ciència de Materials de Barcelona ICMAB–CSIC, Campus UAB s/n, 08193 Bellaterra, Spain
[2]CIBER de Bioingeniería, Biomateriales y Nanomedicina, CIBER-BBN, 08913 Bellaterra, Spain
[3]Servei de Ressonància Magnètica Nuclear, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain
[4]Departament de Bioquímica i Biologia Molecular, Unitat de Bioquímica de Biociències, Edifici Cs, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain.
[5]Institut de Biotecnologia i de Biomedicina (IBB), Universitat Autònoma de Barcelona, Bellaterra, Spain

Contact@E-mail (j.vidal@icmab.es; vega@icmab.es)

Abstract

This abstract focuses on the in vivo applications of radical dendrimer-based Magnetic resonance imaging Contrast Agents (MRI CA) and investigates the factors influencing relaxivity.

MRI, a highly versatile and widely employed clinical diagnostic tool, relies heavily on gadolinium-based contrast agents (GBCAs) for enhancing image quality. These agents work by shortening the T1 relaxation time of nearby water protons, thereby intensifying the signal and contrast between normal and abnormal tissues. [1] However, it's important to note that GBCAs have been associated with the potentially lethal nephrogenic systemic fibrosis for over a decade. [2] In light of this concern, there is growing interest in alternative options, particularly stable organic radicals like nitroxides (e.g., TEMPO, PROXYL). These paramagnetic species can serve as MRI CA similar to Gd(III) chelates but with minimal toxicity. To enhance molecular relaxivity and protect against bio-reduction, one effective approach is anchoring multiple nitroxide units to conventional linear or hyperbranched polymers. Dendrimers with controlled structures are excellent candidates for this purpose. [3] Consequently, we have successfully synthesized a series of free radical dendrimer-based CA characterized by exceptional relaxivity, high water solubility, low toxicity, biocompatibility, and safety. [4]

We have developed a completely organic, metal-free MRI CA (G0 to G3) using polyphosphorhydrazone (PPH) dendrimers, functionalized with up to 48 PROXYL radical units. [4] Notably, G3 demonstrated robust contrast enhancement in murine GL261 glioblastoma tumors, on par with commercial GBCAs. G3 exhibited selective accumulation within brain tumor tissues, extending imaging sessions to over 2.5 hours. Importantly, G3 showed no signs of toxicity and maintained stability within biological environments (Figure 1). [5] All of these features allow us to suggest that radical dendrimers could be a viable alternative to metal-based MRI CA.

Nonetheless, the synthesis of G3 is complex, and our next research focus revolves around simplifying the production of molecules with high relaxivity. The first thing is to simplify the synthesis of dendrimers, and the second is to increase the relaxivity. We have also synthesized fluorescent and magnetic bimodal imaging probes, [6] oligoethylene glycol dendrimers [7] and various other types of radical dendrimers, each exhibiting distinct relaxation rates per nitroxide unit. Understanding the key factors affecting relaxivity is important for the synthesis of good CAs.

Research on the relaxation mechanisms of GBCAs already has theoretical support, [8] such as the SBM theory. [9] However, there are few studies that focus on the relaxation mechanisms of nitroxides especially when they are tethered to macromolecules. Therefore, in this study, we aim to synthesize various types of radical dendrimers and subsequently employ molecular dynamics to investigate the microenvironment surrounding these radicals. We will analyze critical factors including the presence of water molecules, rotational correlation times, molecular configurations, and their impacts on the relaxivity. These discoveries will provide essential theoretical groundwork for future molecular design efforts.

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Figures

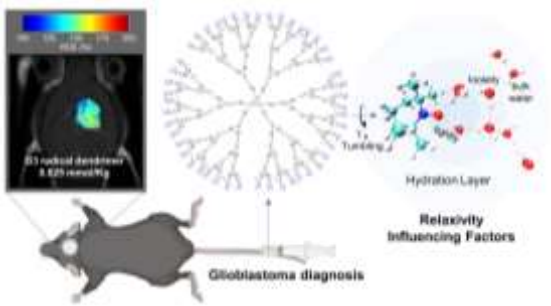

Figure 1. Middle) Structure of G3 based on polyphosphorhydrazone dendrimer and PROXYL (in blue). Left) Color-code scale for relative contrast enhancement (RCE) of GL261 glioblastoma tumour-bearing mice with intravenous administration of G3. Right) Representation of the key factors governing the relaxivity of nitroxides.