MRI tumour detection using metal-free radical dendrimers as contrast agents

Vega Lloveras,[1,2] **José Vidal-Gancedo,**[1,2] Songbai Zhang,[1] Luiz F. Pinto,[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 (vega@icmab.es; j.vidal@icmab.es)

Early detection of tumours is of vital importance to increase the survival ratio of patients. One of the most largely used clinical imaging procedures for the early diagnosis and follow-up of tumors is magnetic resonance imaging (MRI) thanks to its non-radiative and non-invasive character and its capacity of providing images of soft tissue anatomy in excellent detail, when assisted by contrast agents (CAs).

Nowadays, gadolinium-based contrast agents (GBCAs) are far the most widely used MRI contrast agents in clinical practice. GBCAs have historically been considered as safe but for more than a decade, a linear relationship between GBCA administration and the development of potentially lethal nephrogenic systemic fibrosis (NSF) has been recognized in patients with renal impairment.[1] Moreover, newer reports have emerged regarding the accumulation of residual Gd(III) ions in the brain, bones, skin, liver and kidneys of patients with normal renal function and intact blood–brain barrier (BBB).[2] For these reasons, it is critical to find alternative imaging probes to GBCAs to overcome their established toxicity.

Persistent organic radicals are promising alternatives since they also exhibit paramagnetic properties and can act as T_1 CAs like Gd-based CAs while being organic species, mitigating concerns about toxic metal accumulation. With the anchoring of many organic radicals on a dendrimeric macromolecule surface (radical dendrimers)[3] we can achieve an increase of the contrast capacity and protect the radicals from bioreduction, improving the behavior of isolated radicals.

We have successfully synthesized different generations of radical dendrimers fully soluble in water functionalized with nitroxide organic radicals in the periphery. We have demonstrated both *in vitro* and *in vivo* that they can provide similar or even higher contrast enhancement than GBCAs. Under *in vivo* conditions, radical dendrimers have been shown to provide suitable contrast enhancement on murine GL261 glioblastoma (GB) tumors, which was comparable to that of commercial Gd-based CAs, even at its 4 times lower administered dose[3j] (Figure 1). They have showed a selective accumulation in brain tumor tissues, which allows performing imaging acquisition over longer time frames (≥ 2.5 h) than with Gd chelates. No signs of toxicity have been detected and high stability of the radicals in biological media has been observed. All of these features allow us to suggest that radical dendrimers could be a viable alternative to metal-based MRI contrast agents, particularly on MRI analysis of glioblastoma.

References

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Figures

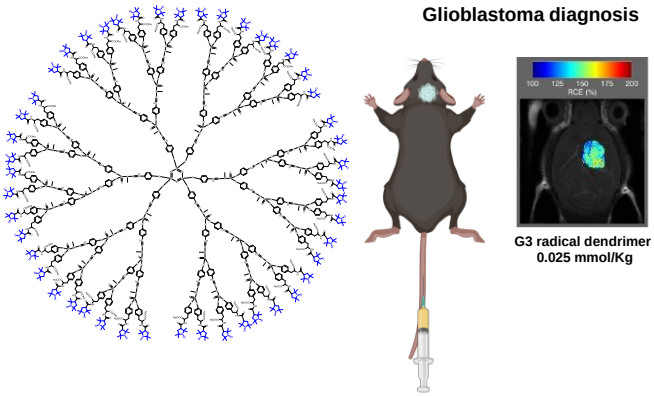

Figure 1. Left) Structure of the third generation of a radical dendrimer based on polyphosphorhydrazone dendrimer and proxyl organic radicals (in blue). Right) Color-code scale for relative contrast enhancement (RCE) of GL261 glioblastoma tumour-bearing mice with intravenous administration of the radical dendrimer.