Hybrid gadolinium oxide nanoparticles: contrast agents combining diagnosis and therapy

Jean-Luc Bridot[1], Anne-Charlotte Faure[1], David Dayde[2], Charlotte Rivière[3], Géraldine Le Duc[4], Claire Billotey[5], Marc Janier[5], Véronique Josserand[6], Jean-Luc Coll[6], Pascal Perriat[7], Stéphane Roux[1] and Olivier Tillement[1]

1 Laboratoire de Physico-Chimie des Matériaux Luminescents, UMR 5620 CNRS – Université Claude Bernard Lyon 1, 69622 Villeurbanne Cedex, France

2 Laboratoire d'immunologie, EA 3853 IPGA Faculté de Médecine, 37032 Tours Cedex, France

3 Nano-H SAS, 23 rue Royale, 69001 Lyon, France

4 European Synchrotron Radiation Facility, 6 rue Jules Horowitz, BP220, 38043 Grenoble Cedex, France

5 Laboratoire CREATIS – Animage, UMR 5515 CNRS - U630 INSERM - INSA de Lyon - Université Claude Bernard Lyon 1, 69622 Villeurbanne Cedex, France

6 Groupe de Recherche sur le Cancer du Poumon, INSERM U578, Institut Albert Bonniot, 38706 La Tronche Cedex, France

7 MATEIS, UMR 5510 CNRS - INSA de Lyon, 69621 Villeurbanne Cedex, France

Keywords: gadolinium oxide nanoparticles, magnetic resonance imaging, neutron capture therapy, X-ray therapy

Abstract

The synthesis of gadolinium oxide nanoparticles embedded in a fluorescent polysiloxane shell constitutes an attractive way for combining imaging and therapy. The presence of gadolinium ions in the core allows monitoring their biodistribution after intravenous injection in small animals by magnetic resonance imaging (MRI). They can be also followed up by fluorescence imaging since organic dyes are covalently bound in the polysiloxane shell. Although these particles are harmless, their irradiation by thermal neutrons or by X-rays led to the destruction of cancerous cells or of tumors.

Rationale and objectives

The intense research activities devoted to the nanoparticles during the last decade have opened the door to promising biological and medical applications. Besides their reduced size which makes them suitable for labeling biomolecules or for exploring the living machinery at the sub-cellular scale without functional alteration, the great potential of the nanoparticles rests on the ability to gather in a same object several complementary properties. Recently we demonstrated that Gd^{3+} based crystalline nanoparticles can reduce significantly the longitudinal relaxation time of water proton [1]. In this study we have prepared and characterized luminescent hybrid nanoparticles containing a gadolinium oxide core for in vivo imaging and therapy.

Methods

synthesis of multifunctional gadolinium oxide nanoparticles, in vivo imaging (magnetic resonance imaging (MRI), fluorescence imaging), neutron capture therapy, microbeam radiation therapy.

Results

The hybrid nanoparticles were synthesized by embedding a gadolinium oxide core in a luminescent polysiloxane shell [2]. These luminescent particles were functionalized by

weak molecular weight PEG which improves the colloidal stability in aqueous media. Despite the presence of the polysiloxane shell, hybrid particles are able to exert an influence on the water proton relaxation. As compared to Gd-DOTA, the longitudinal relaxivity r_1 of the particles are higher for same gadolinium content (8.8 $s^{-1}.mM^{-1}$ versus 4.1 $s^{-1}.mM^{-1}$) [1].

These particles can be internalized by different cell types (macrophages, fibroblasts, lymphocytes…). As a result, the labeled cells can be visualized by MRI and fluorescence imaging. If the metabolic activity of the cells is almost not affected by the presence of the hybrid particles, cells after internalization of the particles were killed when submitted to a thermal neutron beam whereas its innocuousness was attested. This experiment reveals consequently the therapeutic potential of gadolinium oxide nanoparticles for the cancer therapy by neutron capture.

The circulation of these particles after intravenous injection in mice and rats can also be monitored by fluorescence and magnetic resonance imaging. Both techniques reveal that there is no undesirable accumulation in lungs, liver, spleen and brain: they freely circulate in the blood vessels before being eliminated by renal excretion. This behavior is attributed both to the small size of the hybrid particles (< 10 nm) and to the presence of PEG chains tethered to the particles. However accumulation is observed in brain for rats bearing tumor in brain. This was exploited for treating the tumor with X-ray beam. The irradiation of tumor bearing rats with X-ray microbeam 20 minutes after the injection of fluorescent hybrid gadolinium nanoparticles led to a longer survival of the rats.

Conclusion

Gadolinium oxide nanoparticles embedded in a pegylated and luminescent polysiloxane shell are very attractive since they are well suited for in vivo dual modality magnetic resonance and fluorescence imaging and they induce cell or tumor death after irradiation. These particles are expected to combine diagnosis and cancer therapy.

References

[1] Bridot JL, Faure AC, Laurent S, Rivière C, Billotey C, Hiba B, Janier M, Josserand V, Coll JL, Vander Elst L, Muller R, Roux S, Perriat P, Tillement O, *J. Am. Chem. Soc.* **2007**, *129*, 5076-5084.

[2] Louis C, Bazzi R, Marquette CA, Bridot JL, Roux S, Ledoux G, Mercier B, Blum L, Perriat P, Tillement O. *Chem. Mater.* **2005**, *17*, 1673-1682.