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An optoactive polyglycerol dendrimer for enhanced tumor imaging

A. A. A. De Queiroz[(1)*], M. A. P. Camillo[(2)], O.Z. Higa[(2)]

(1) Departamento de Física e Química/Instituto de Ciências Exatas, Universidade Federal de Itajubá (Unifei), e-mail: alvaro.alencar@pq.cnpq.br
(2) Centro de Biotecnologia, Instituto de Pesquisas Energéticas e Nucleares (IPEN), e-mail: mcamillo@ipen.br, ozahiga@ipen.br.
* Corresponding author.

Abstract – In this work the synthesis and characterization of the gadolinium−rhodamine polyglycerol dendrimers is reported. PGLD with generation 3 (G3.0) was synthesized by step-by-step allylation and dihydroxylation reactions. Rhodamine was functionalized for the coupling reaction with PGLD. Tumor cells were inoculated subcutaneously into the flanks of C3H mice and the PGLD optodendrimer have been able to image these labeled tumor cells via magnetic resonance and optical imaging. Furthermore, it was possible to visualize the labeled tumor cells via fluorescent microscopy after tissue biopsy. Our results suggest that these optodendrimers could be useful in cancer imaging and diagnosis.

Optical molecular imaging in combination with nanobiotechnology is emerging as a powerful tool for studying the temporal and spatial dynamics of tumor cells. Using exogenous targeted probes, researchers can now perform non-invasive studies on living systems and visualize the imaging of receptor expression and/or activity over time might have greater potential for treatment decisions based on early molecular response assessment. Optical imaging using fluorescent techniques represents a promising approach since it is inexpensive and involves no exposure to ionizing radiation, providing spatiotemporal resolution on the basis of relatively small data sets compared with other conventional imaging methods [1]. In this work the synthesis and characterization of the gadolinium−rhodamine polyglycerol dendrimers (RhB-PGLD-Gd^{3+}) is reported. PGLD is a class of novel nano-scaled polymers with spherical and has well-defined tree-like structures with extraordinary symmetry, high branching and maximized terminal functionality density [2]. The unique molecular features and properties of PGLD, like multiple reactive chain ends, their excellent water solubility and biocompatibility renders them as valuable compounds for molecular imaging in medicine applications.

The PGLD of generation 3 (G3.0) was synthesized by divergent method towards a repetitive sequence of allylation and catalytic dihydroxylation steps in according to literature [3] and was partially terminated with 2-(4-isothiocyanatobenzyl)-6-methyldiethylenetriaminepentaacetic acid (DPTA) chelating groups for gadolinium ion coordination. Reactive aldehyde groups on PGLD were prepared by Schimdt reaction for the rhodamine B (RhB) coupling. The activated PGLD was labeled with RhB by reacting G3.0 PGLD with rhodamine B isothiocyanate.

The RhB-PGLD-Gd^{3+} had a monodispersed molecular weight, characterized by matrix-assisted laser-desorption-ionization time-of-flight mass spectroscopy (MALDI-TOF) and size-exclusion chromatography (SEC). The MALDI-TOF mass spectrum for RhB-PGLD-Gd^{3+} showed the signal peak at m/z =1,560. This value was in good agreement with the expected molecular weight of 1,533. From SEC measurements, RhB-PGLD-Gd^{3+} had a narrow peak, from which the purity was determined to be 99.2%. On a G3.0 PGLD generation there are 24 hydroxyl groups, some (approximately 4) of which was used to attach RhB rhodamine labels. The absorption and fluorescence spectra indicated that the cored RhB in the PGLD behaved as a single-like molecule with little dipole-dipole interaction between chromophores, and chromophores and local environment at the ground state. The time resolved fluorescence decay measurements indicated that RhB-PGLD-Gd^{3+} emitted fluorescence through a spontaneous emission from one species. The decay constant steady state fluorescence of RhB-PGLD- Gd^{3+} was estimated to be 4.1 ns and was dependent of the solvent polarity. Analysis of NMR spectroscopy data revealed that the targeted imaging agent (Rh-PGLD-Gd^{3+}) was loaded with 7.0% of Gd^{3+}. The relaxivity of Gd dendrimer was measured and found to be 16.8 ± 0.2 $s^{-1}mM^{-1}$. Tumor cells in animal model were inoculated subcutaneously into the flanks of C3H mice and the PGLD optodendrimer have been able to image these labeled tumor cells via magnetic resonance and optical imaging. MRI images of tumor showed an increase of uptake within 24h with a higher retention of targeted Rh-PGLD-Gd^{3+} in tumor tissue.

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