SOLUBLE GD(III)DOTA ADDUCTS WITH MULTIWALLED CARBON NANOTUBES AS NOVEL CONTRAST AGENTS FOR DIFFUSION TENSOR IMAGING

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Introduction. Effectiveness of diagnosis by MRI involves not only the design of more efficient MR sequences but the development of improved Contrast Agents (CAs) increasing the quality, resolution and specificity of the MR images.[1-3] Classical contrast agents and MRI methods remain unable to establish the spatial orientation of microvascular blood flow. Our previous work, demonstrated the use of carbon nanotube preparations and diffusion weighted MR imaging methods to investigate the preferred orientation of water flow.[4] However, these early preparations depicted reduced paramagnetic character and remarkably small solubility. We describe here a new generation of highly soluble, paramagnetically labeled multiwall CNTs (MWCNTs) with Gd(III)DOTA monoamide-like functionalized with a pyrene moiety, linked to the CNT through π–π stacking interactions. In particular, we report on the synthesis, MRI studies (ADC, T1, T2) and fluorescence emission spectra of these π–π stacking MWCNTs-pyrene DOTAma adducts.

Materials and methods. We employed commercial MWCNTs (SES Research, Houston, TX, USA), <10 nm diameter, 1-5 micron average, fragmented by horn-ultrasonication (100 hours) in Toluene, investigating the resulting length by TEM (200 kV).[5] We used 1-Pyrenebutyric acid N-hydroxysuccinimide ester derivatives, linked to a Gd(III) ligand (DOTA monoamide like) through two different spacers: 4,7,10 trioxadodecandiamine (PEG) and ethylendiamine.[6,7] We formed the corresponding Gd(III) complexes from the two different derivatives (pH=7) and obtained new adducts with the shortened-MWNTs in water by π–π stacking interaction (Fig1A, C). Fluorescence studies (Fig 1B): emission spectra recorded at 25°C, pH = 7.2, in water (λ_{exc}= 340 nm), Gd(III) complexes concentration was 10^{-6} mM, π–π stacking adducts concentration: 5 *10^{-7} mg/mL.[8] MRI studies: MWCNTs adducts in water (1 mg/mL, pH= 7.2) were placed in an Eppendorff tube (2 mL) accommodated to polystyrene adapter and placed in the center of the magnetic field of a Bruker Pharmascan 7 Tesla scanner (Bruker Daltonics, Ettlingen, DE).[5] We measured: T_1 (RARE VTR), T_2 Maps (MSME) and three ADC Maps (diffusion-weighted spin–echo sequence with echo planar readout), with the diffusion-encoding gradient oriented in the H–F (B_0), L–R, or A–P orthogonal directions, respectively.

Results.

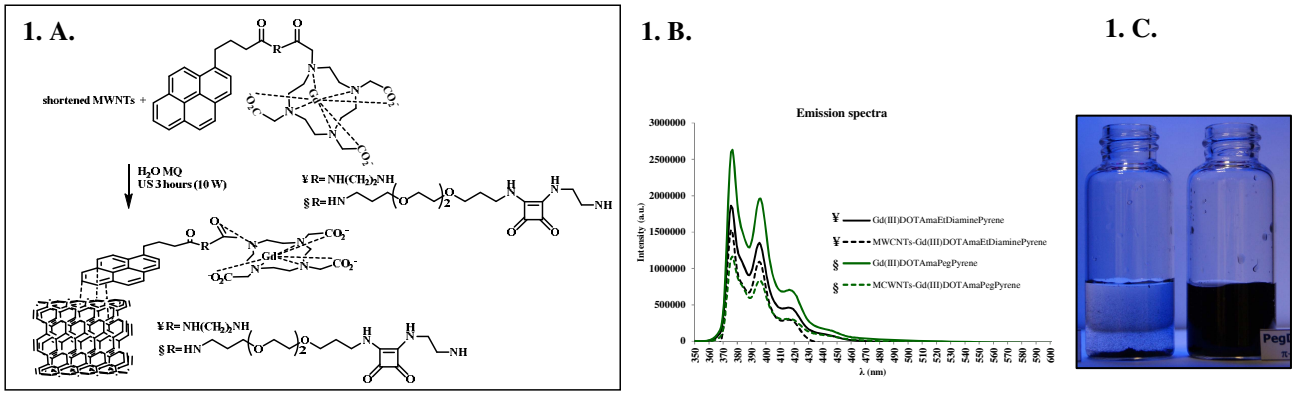

Figure1:A. π–π stacking adduct formation between Gd(III) DOTAmaPegPyrene (§), Gd(III)DOTAmaEtDiaminePyrene (¥) complexes and MWCNTs shortened (US horn 100 hours) in water. B. Fluorescence Emission spectra of Gd(III) complexes (solid) and π–π stacking adducts (dotted). All samples show three emission maxima at 370, 395 and 415 nm. C. Left: MWCNTs (US horn 100 hrs) in water, note insolubility, right: π–π stacking adduct MWCNTs-Gd(III)DOTAmaPegPyrene (§), note solubility.

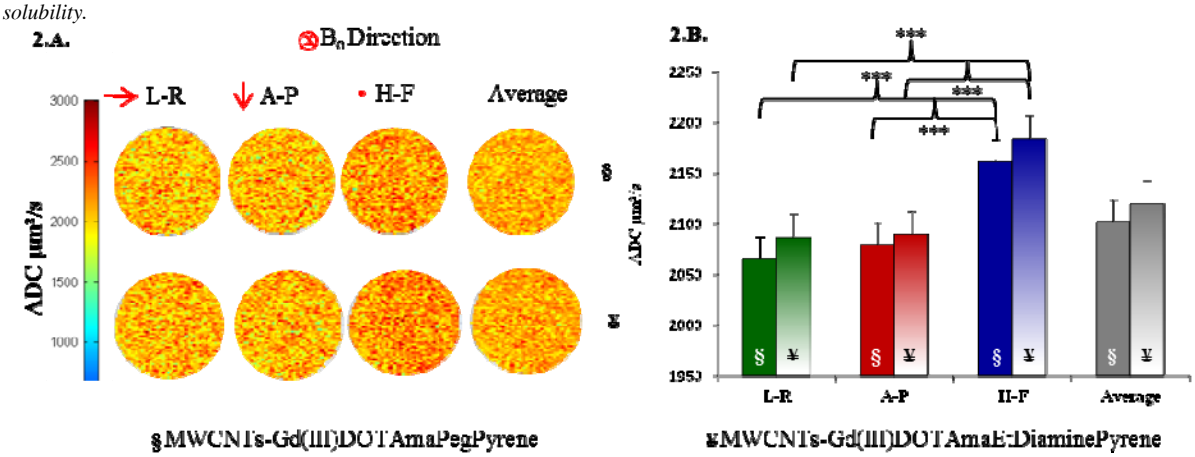

Figure2: A. ADC maps of MWCNTs- Gd(III) DOTAmaPegPyrene (§) and MWCNTs- Gd(III)DOTAmaEtDiaminePyrene (¥). Note that water ADC is significantly higher along the B_0 direction (H–F) than in the perpendicular plane (A–P or L–R directions). B. Bar graphs depict ADC values of § and ¥ adducts (mean ± standard error) measured in slices 1–3 with the diffusion-encoding gradient oriented in the L–R (green), A–P (red), or H–F (blue) directions. Average ADC in three directions (grey).

Conclusions: We synthesized two different π–π stacking adducts MWNTs-Gd(III)DOTAmaPyrene and MWNTs-Gd(III)DOTAmaEtDiaminePyrene, shown to be highly water soluble and to induce anisotropic diffusion of water, due to alignment of the magnetic nanotubes along the B_0 axis. These derivatives are also potential fluorescence probes yielding a novel multimodal imaging platform.

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