Cy5.5-Labeled and gadolinium-chelated chitosan nanoparticles

Cy5.5-CNP-Gd(III)

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Chemical name:	Cy5.5-Labeled and gadolinium-chelated chitosan nanoparticles	
Abbreviated name:	Cy5.5-CNP-Gd(III)	
Synonym:		
Agent Category:	Nanoparticles	
Target:	Non-targeted	
Target Category:	Non-targeted	
Method of detection:	Multimodality imaging (optical/magnetic resonance imaging (OI/MRI))	
Source of signal / contrast:	Cy5.5 and Gd(III)	
Activation:	No	
Studies:	• *In vitro* • Rodents	No structure is available.

Background

[PubMed]

The Cy5.5-labeled and gadolinium (Gd(III))-chelated chitosan nanoparticles, abbreviated as Cy5.5-CNP-Gd(III), are an optical/magnetic resonance (MR) dual imaging agent synthesized by Nam et al. for multimodality imaging of tumors (1).

The idea of using multiple modalities in a single imaging session comes from the fact that modalities with high sensitivity have relatively poor resolution, while those with high resolution have relatively poor sensitivity (2, 3). Integration of multiple modalities in

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imaging would take the advantages of each modality and allow better characterization of diseases and disease processes (4, 5). To date, the most successful hybrid system is derived from the fusion of positron emission tomography (PET) and computed tomography (CT) (5-8). PET is highly sensitive and allows three-dimensional images that show the concentration and location of the radiolabeled tracers of interest, while CT provides high-resolution imaging of the anatomical structures. Because of limited soft-tissue contrast and high X-ray radiation that accompanies CT imaging, considerable effort has been invested in recent years toward development of PET/magnetic resonance imaging (MRI) hybrid systems in an attempt to generate combined functional and morphological images with excellent soft tissue contrast, good spatial resolution of the anatomy, and accurate temporal and spatial image fusion (9-11). In contrast, systems integrated with optical techniques have not been investigated as extensively. Considering the advantages of multichannel imaging with single or multiple probes and the low cost of studying reporter gene expression in animal models, optical imaging integrated with other modalities may provide information at the cellular and molecular levels, which is critical in preclinical studies (1, 2, 12).

Development of hybrid imaging technology has triggered great effort in probe development to boost the benefits of hybrid instrument technology (12-15). In the case of optical/MRI probe design, the challenge is turned around to incorporate enough paramagnetic ions for detection by the relatively low sensitivity of MRI. Nam et al. have developed a dual imaging probe (Cy5.5-CNP-Gd(III)) with water-soluble glycol chitosan and the probes were preferably accumulated within the tumor xenografts *in vivo* (1). Chitosan has been frequently used to make nanoparticles carrying imaging reporters as well as therapeutic agents (1, 12, 15). Generally, the positively charged chitosan polymer can coat around a nanoparticle core by electrostatic adsorption, and other components are embedded in the chitosan matrix during the coating process. All components can also be entrapped simultaneously in the chitosan matrix.

Related Resource Links:

- Multimodality imaging agents in MICAD
- Multimodality imaging clinical trials in ClinicalTrial.gov

Synthesis

[PubMed]

Nam et al. synthesized Cy5.5-CNP-Gd(III) by conjugating Cy5.5 to amphiphilic glycol chitosan (GC)-5β-cholanic acid (CA) conjugates (Cy5.5-GC-CA) and chelating Gd(III) with 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-modified Cy5.5-GC-CA conjugates (1). Briefly, biocompatible and water-soluble GC (50 kDa) was first chemically modified with CA to form an amide linkage between the amine group of GC and the carboxyl acid of CA, resulting in the GC-CA conjugate. The molecular weight of GC-CA was 54 kDa with 11 ± 2 CA molecules per GC. For optical imaging, 0.5 ± 0.1 dyes

of Cy5.5 monohydroxysuccinimide ester were then conjugated to the GC-CA (Cy5.5-GC-CA). For MRI, DOTA was first directly conjugated to the amine groups in the Cy5.5-GC-CA, and Gd(III) was then chelated. The degree of substitution of the number of DOTA molecules per nanoparticle was in the range from 13 to 45. The weight ratio of Gd(III) was maximized to ~6 ± 0.28%. The Cy5.5-CNP-Gd(III) nanoparticles were spherical in shape and ~350 nm in diameter. In phosphate-buffered saline at 37°C, Cy5.5-CNP-Gd(III) nanoparticles remained dispersed and maintained their original size for up to 40 days. Strong fluorescent signals and identical T1-weighted images were obtained under different pH conditions (pH 5.2 and 7.4). These results indicate that the chelated Gd(III) ions are highly stable in the nanoparticles.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The cellular uptake and cytotoxicity of Cy5.5-CNP-Gd(III) were evaluated *in vitro* with HeLa H2B-GFP cells (1). After incubation of the cells with Cy5.5-CNP-Gd(III) for 1 h, Cy5.5-CNP-Gd(III) nanoparticles were rapidly taken up by the HeLa cells and were found in the cytoplasm of cells. Cy5.5-CNP-Gd(III) exhibited almost 100% cell viability even at relatively high concentrations up to 250 μg/ml after incubation for 24 h.

Animal Studies

Rodents

[PubMed]

Biodistribution of Cy5.5-CNP-Gd(III) was analyzed with optical imaging after intravenous injection into nude mice bearing subcutaneous tumors of murine squamous carcinoma cells (SCC7) (1). Mice treated with Cy5.5-CNP-Gd(III) (n = 3 mice; 5 mg/kg) showed a strong near-infrared fluorescence (NIRF) signal throughout the whole body within 6 h after injection. Tumors were able to be delineated from the surrounding tissue from 6 h, exhibited the maximum NIRF signal from 12 h to 3 days, and were still visible for up to 5 days after injection. *Ex vivo* images of the excised tissues 1 day after injection showed that Cy5.5-CNP-Gd(III) was mainly taken up by the tumors and was not significantly taken up by normal tissues. The total photon counts per gram of each organ were three- to seven-fold higher in tumors than in other organs (liver, lungs, kidneys, heart, and tumors). Approximately 50% of the nanoparticles circulated for 23 h, indicating a prolonged blood lifetime.

Optical/MR dual imaging was also performed in the SCC7 tumor-bearing mice (1). Both NIRF optical and MRI (1.5 T) readily detected the tumors at 1 day after injection of Cy5.5-CNP-Gd(III) (5 mg/kg). With T1-weighted imaging, the margin of the tumor tissue could be clearly delineated, indicating efficient nanoparticle accumulation at the tumor site. After 1 day, the relative signal enhancement (%) of tumors strongly increased from 70

to 162, compared with that of muscles (65 to 95), indicating that the nanoparticles had greater tumor targeting ability.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

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