Cross-linked iron oxide-Cy5.5

CLIO-Cy5.5

The MICAD Research Team

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Chemical name:	Cross-linked iron oxide-Cy5.5	
Abbreviated name:	CLIO-Cy5.5	
Synonym:		
Agent Category:	Iron oxide	
Target:	Phagocyte and tumor cell	
Target Category:	Endocytosis	
Method of detection:	Magnetic resonance (MRI), Optical (NIRF)	
Source of signal:	Iron oxide, Cy5.5	
Activation:	No	
Studies:	• *In vitro* • Rodents	Click on the above structure for additional information in PubChem.

Background

[PubMed]

Complete resection is critical in terms of survival of brain tumor populations (1). Consequently, accurate delineation of tumor margins is critical to the successful surgical resection of brain tumors. It is important to relate the preoperative radiological images to the visual presentation of pathology during surgery. There are several such visible wavelength-emitting optical agents as fluorecein (2), indocyanine green (3), and porphyrin (4, 5) have been used to provide intraoperative fluorescence images in the tumor region. However, they have not been widely accepted as providing accurate tumor boundary because of the limited circulation time, mediocre signal-to-noise ratio, and readily diffuse into and out of the interstitial space. Other low molecular weight agents such as gadolinium chelates have been applied to obtain the contrast-enhanced magnetic resonance (MR) image, but they were not very useful intraoperatively because the distribution was not constant over the hours required by tumor resection. Hence it is of

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interest to develop a reagent that provides preoperative MR image which can be visualized intraoperatively.

A multimodal nanoparticle probe that consists of a contrasting agent (for preoperative MR image) and a near infrared (NIR) fluorochrome (for intraoperative visualization) may provide consistent information both preoperatively and intraoperatively. Superparamagnetic iron oxide nanoparticles such as MION and CLIO can be internalized by cells of reticuloendothelial system and have long circulating time within animal body. Therefore, it can accumulate in the brain tumors (6). The blood half-life of MION in human is about 24 hours (7) and the blood half-lives of both CLIO-NH_2 and MION are about 10 hours in mice (8). The accumulation of nanoparticles in cells cause reduction in signal intensity with T2-weighted spin echo pulse sequences. These nanoparticles thus become a good choice to be administered before the surgery for MR images. Compare to visible wavelength-emitting fluorochromes, NIR fluorochrome (e.g. Cy5.5) provides improved light transmission through tissue and decreases the effect, hence the background, of autofluorescence from brain tissue (9). Near Infrared fluorescence (NIRF) also provides simultaneous full-color spectrum white light imaging while acquiring and displaying fluorescence separately (10).

CLIO-Cy5.5 (1, 9) is a multimodal agent that consists of a superparamagnetic iron oxide nanoparticle (CLIO) and a NIR fluorochrome (Cy5.5). It serves as a contrast agent for preoperative MRI to visualize the brain tumor and, in the meantime, provides an intraoperative NIR fluorescence image that discriminate tumor from normal brain tissue because of the phagocytic function of tumor cells. This nanoparticle is internalized by cells before surgery begins and does not diffuse out of the cells or through the interstitial space during the surgery, consequently, it could be a useful agent which provides consistent information before and during the brain tumor resection.

Synthesis

[PubMed]

The synthesis of CLIO-Cy5.5 was described by Kircher et al. (9). In brief, 0.2 mL of CLIO-NH_2 nanoparticle (produced by mixing CLIO nanoparticles with dextran, followed by activation with epichlorohydrin and ammonia (11, 12), at a concentration of 10 mg Fe/mL in a citrate buffer (20 mM, pH 8) was mixed with Cy5.5 solution at room temperature for 2 h, followed by incubation at 4°C overnight. Excess Cy5.5 was removed by gel filtration using a Sephadex G-25 column in a citrate buffer (20 mM, 150mM NaCl, pH 8). The size of the nanoparticle was determined to be 32 nm using laser light scattering method and had an average of 1 Cy5.5 dye per iron oxide crystal.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

No relevant publication is currently available.

Animal Studies

Rodents

[PubMed]

The study of brain tumor delineation by CLIO-Cy5.5 was performed by injecting the 9L rat gliosarcoma cell line transfected to express GFP (9L-GFP-cell) into Fischer 344 rats (9). MRI of rat was performed 10-14 days after tumor inoculation. Cy5.5-CLIO (15 mg/kg) was introduced into animals through tail vein injection and MRI was performed 24 h after the injection. The distribution of tumor in the brain was determined by fluorescence of GFP and Cy5.5 on the cryosectioned tumors. High congruency of tumor extent was observed between the MR image and the H&E staining. The accumulation of iron was demonstrated by DAB-amplified Prussian blue stain. Twenty-five slices of five brain tumors were analyzed by comparing both Cy5.5 and GFP positive area. The data was fitted with linear regression. It showed a slope of 1.013, and intercept of 0.820 mm^2, and a R^2 of 0.996. The over estimation by Cy5.5 compared to the tumor delineation by GFP fluorescence was caused by the uptake of CLIO-Cy5.5 by microglia.

Hosts with different immune responses to the tumor were used to further asses the accuracy of brain tumor delineation by CLIO-Cy5.5. GFP expressing tumor cells were implanted in Wistar male rate and female nude mice (1). Images were taken after 7-10 days of inoculation. CLIO-Cy5.5 (15 mg/kg) was administered through tail vein injection and MR images were taken 24 h after the introduction of CLIO-Cy5.5. A threshold method was applied to determine the boundary of tumors. The average overestimation of CLIO-Cy5.5 border was 0.02 mm in the rat and 0.002 mm in nude mouse compared to the GFP border (which indicated the tumor extent). The maximum overestimation was 65 and 151 μm, respectively, and the maximum underestimation was 64 and 57 μm, respectively, for mice and rat. These were within a few cell diameters of the true tumor boundary. CLIO-Cy5.5 nanoparticles were internalized by microglia/macrophages at the periphery of the tumor and the tumor cells. There was no uptake of the nanoparticle by astrocytes.

Other Non-Primate Mammals

[PubMed]

No publication is currently available.

Non-Human Primates

[PubMed]

No publication is currently available.

Human Studies

[PubMed]

No relevant publication is currently available.

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