Reconstituted HDL for PARACEST-fluorescence multimodal imaging

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Introduction A novel reconstituted high-density lipoprotein (rHDL) nanocomposite[1] has been prepared for high-sensitive magnetic resonance (MR)-fluorescence multimodal imaging (Fig. 1). Such nanocomposite is able to enhance the MR sensitivity up to 129 folds in comparison to the traditional small molecule MRI agent based on paramagnetic chemical exchange saturation transfer (PARACEST). The high-payload of PARACEST agents can improve the CEST detection sensitivity. Therefore, the development of a high-payload, dual-modality MRI contrast agent would have good utility for the detection of atherosclerotic plaques, and may improve treatment planning.

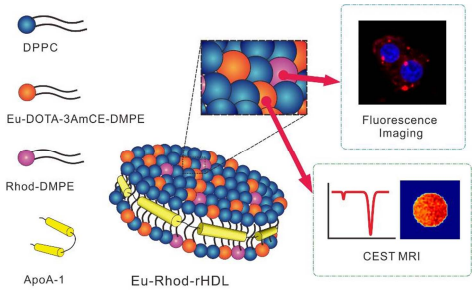

Fig. 1 Preparation of dual-modal contrast agent Eu-Rhod-rHDL

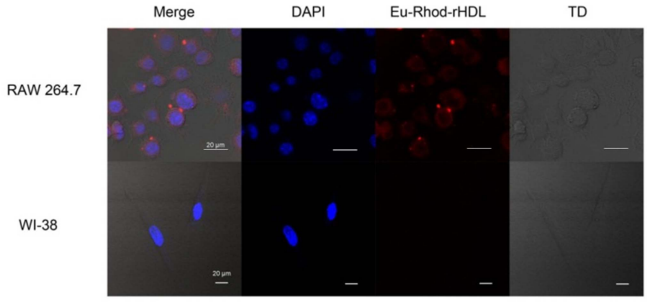

Fig. 2 The LSCM images of macrophages and normal cells

Methods The PARACEST MR-fluorescence Eu-Rhod-rHDL was prepared via a self-assembly process of phospholipids and apolipoprotein ApoA-I. The CEST Z-spectra were acquired with a selective saturation pulse at 25 μT for 5 s. The CEST images were conducted using a FLASH pulse sequence (T_R=5012 ms, TE= 6 ms, matrix 128×128, field of view 20×20 mm^2, slice thickness 4 mm, one average) preceded by a 8 μT selective saturation pulse at 50 ppm centered on the bulk water frequency for 5 s. The detection of macrophage was investigated by laser scanning confocal microscopy (LSCM).

Results and Discussion The number of Eu (III) per Eu-Rhod-rHDL particle was ~155, determined by the ratio of the concentration of Eu (III) and ApoA-I. After incubation, the Eu-Rhod-rHDL, represented by red color indicated by the rhodamine on the particle, can be clearly observed in the cytoplasm in the macrophages in the LSCM images, while almost none observed of the normal cells (Fig. 2). These results clarified that more Eu-Rhod-rHDL entered macrophages in the incubation process, while little entered the normal cells. The CEST Z-spectra of Eu-Rhod-rHDL showed 9 % CEST effect at the concentration of 77.4 μM (Fig. 3). Same CEST effects were observed in the small molecular agent Eu-DOTA-4AmCE. Accordingly, the sensitivity was improved in about 129 folds (on per particle basis) with 155 Eu-labeled phospholipids on the Eu-Rhod-rHDL. Meanwhile, the CEST MR image showed a mean 8% CEST effect (Fig. 4).

Conclusion The Eu-Rhod-rHDL was shown a 129 folds sensitivity enhancement of the CEST effect than the conventional small molecule agent. It can be exploited not only for MRI but also for fluorescent imaging. The rHDL nanoparticles specific uptake by macrophages shows great potential in the detection of atherosclerosis using such nanocomposite.

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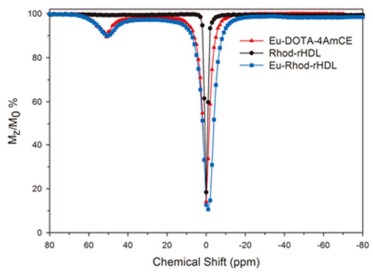

Fig.3 The Z-spectra of Eu-Rhod-rHDL, and small molecule agent Eu-DOTA-4AmCE, which generated same CEST effect

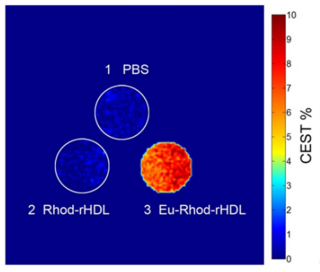

Fig.4 CEST MRI of (1) PBS at pH 7.4, (2) Rhod-rHDL and (3)Eu-Rhod-rHDL