GdAAZTA-C17 (q=2) Labeled High Density Lipoproteins (HDL) for the In Vivo Detection of Atherosclerotic Plaque

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Introduction: High-density lipoproteins (HDL) have emerged as potential therapeutic targets and diagnostic agents for the treatment and detection of cardiovascular disease. Native HDL is a nanoparticle consisting of phospholipid monolayer, a hydrophobic core, and Apolipoprotein (ApoA-I) that interacts with liver hepatocytes and intraplaque macrophages. Preliminary studies have shown that incorporation of gadolinium labeled lipids into the lipid core of native HDL results in the formation of biocompatible molecular imaging probes that allow for the identification and assessment of intraplaque macrophages by magnetic resonance imaging (MRI). High relaxivity gadolinium chelates (GdAAZTA) have recently been developed that increase the longitudinal relaxivity by increasing the number of water exchange sites (q) available to water protons. The aim of the current study was to investigate the MR imaging efficacy of q=1 GdDTPA-DMPE and q=2 $GdAAZTAC_{17}$ labeled HDL in ApoE-/- mouse models of atherosclerosis.

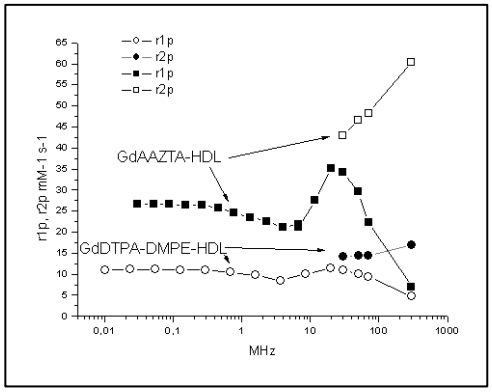

Fig.1: NMRD profile of q=1 and q=2 HDL in aqueous solution.

Methods: Human HDL was labeled with either GdDTPA-DMPE (q=1) or $GdAAZTAC_{17}$ (q=2) using established incubation methods. The particles were characterized with respect to size and relaxation properties. Titration studies were performed to determine the thermodynamic association constants and number of binding sites. MRI was performed at 9.4T over a 72-120 hour time interval after administration of both a 0.018 mmol and a 0.048 mmol Gd/kg dose of q=1 or q=2 labeled HDL to apoE KO mice.

Results: The r1 of q=2 labeled HDL was 3.4 times greater than that of GdDTPA-DMPE HDL at 20 MHz, as shown in **Fig.1**. The mean hydrated diameter of the q=1 and q=2 HDL particles was 15 and 10.8 nm, respectively. Titration studies indicate that the q=1 lipid forms a micelle prior to the association with HDL, as shown in **Fig.2**. The thermodynamic association constant (ka) and number of binding sites (n) were ka=<4000 and ka=70,000 and n=2000 and n=80 for the q=1 and q=2 HDL adducts, respectively. The variation in the binding between the lipids and HDL is related the critical micellular concentration (CMC) associated with the lipid formulations tested. GdDTPA-DMPE has a low CMC value (not detectable by relaxometry) and forms micelles prior to association. The higher CMC of $GdAAZTAC_{17}$ allows for integration of the lipid into the core. These findings were confirmed by titration in the presence of beta-cyclodextran (inhibits micelle formation). MRI in ApoE-/- indicates that the arterial wall enhancement (%NENH) observed for GdDTPA-DMPE labeled HDL at a dose of 0.048 mmol Gd/kg is similar to enchant observed following a 0.018 mmol Gd/kg dose of $GdAAZTAC_{17}$ labeled HDL (**Fig.3)**.

Conclusions: $GdAAZTA\text{-}C_{17}$ labeled HDL may allow for *in vivo* detection of intraplaque macrophages at lower gadolinium doses, when compared to GdDTPA-DMPE HDL.

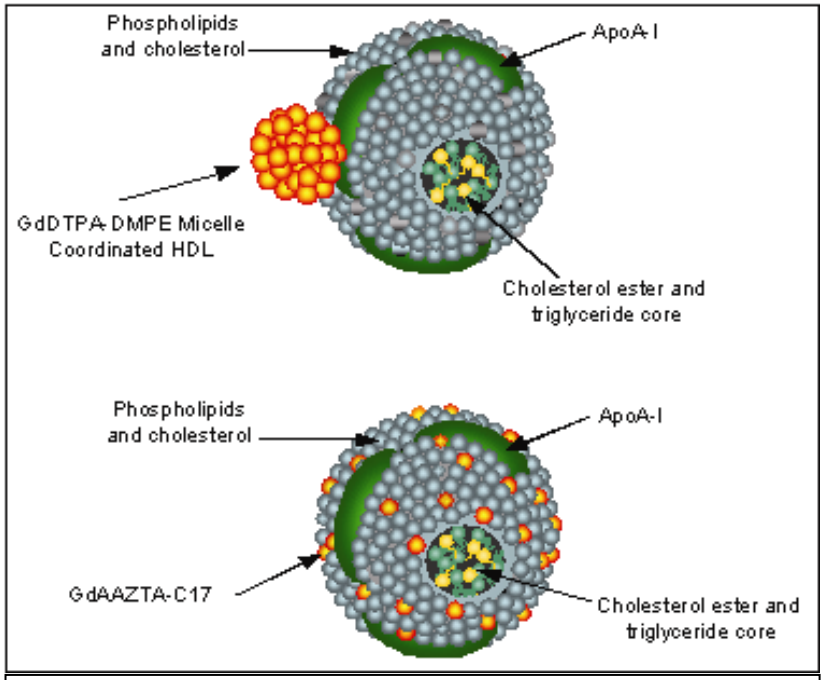

Fig2: Schematic diagram of HDL adducts formed.

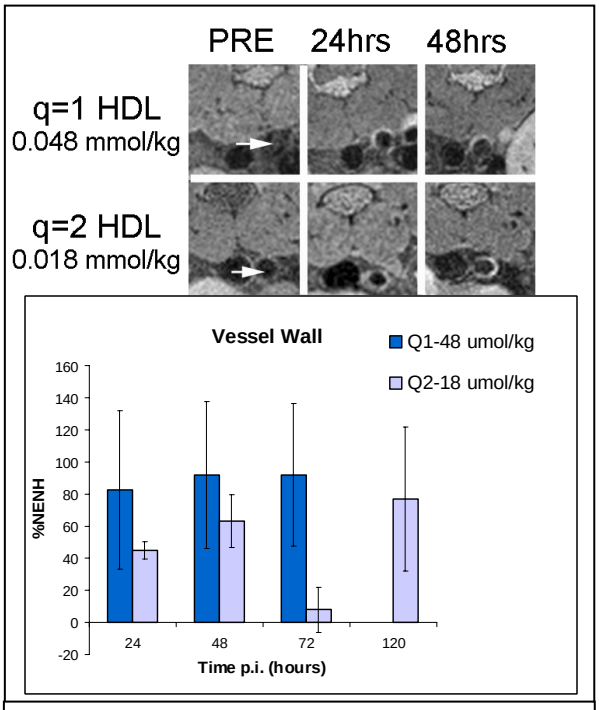

Fig.3: MR enhancement in the arterial vessel wall.