

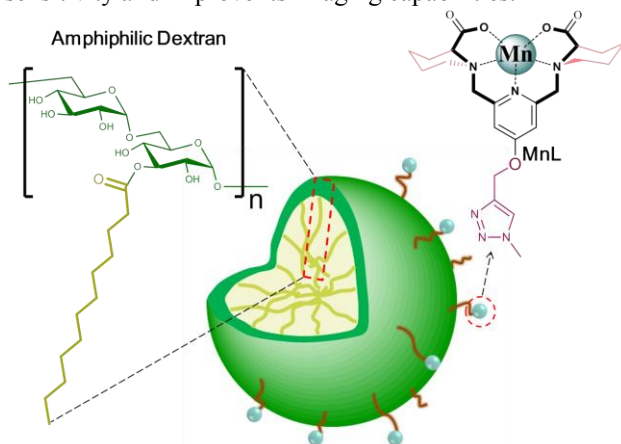
Multivalent Manganese Complexes Decorated Amphiphilic Dextran Micelles as Sensitive MRI Probes

Changqiang Wu¹, Danyang Li¹, Bingbing Lin¹, Chunchao Xia², Qiyong Gong², Bin Song², Hua Ai^{1,2*}

1. National Engineering Research Center for Biomaterials, Sichuan University, Chengdu, PR China

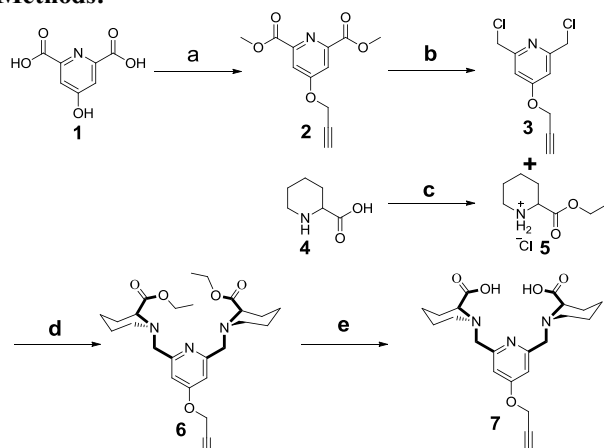
2. Department of Radiology, West China Hospital, Sichuan University, Chengdu, PR China

Statement of Purpose: Administration of Gd-based MRI contrast agent can generate serious side effects such as nephrogenic systemic fibrosis (NSF) in some patients¹. Manganese (II) has five unpaired electrons, slow electron relaxation, fast water exchange rate, and lower intrinsic toxicity than Gd³⁺, which makes it an attractive alternative of gadolinium (III) for enhanced MRI applications. In our previous work², we designed a new manganese complex (MnL), which has better contrast over traditional commercial contrast agent. Here, we do functional modification of the manganese complex, and connect it on the surface of polymeric micelles of amphiphilic dextran (Scheme 1), which is hydrophilicity, biodegradability and biocompatibility, to increase the sensitivity and improve its imaging capabilities.



Scheme 1. Schematic illustration of the multivalent MnL decorated amphiphilic dextran micelles.

Methods:



Scheme 2. Synthesis of the ligand with alkyne group. a) i) HCl, MeOH, reflux, ii) BrCH₂CH₂CH₂, K₂CO₃, CH₃CN, reflux; b) i) NaBH₄, EtOH, reflux 5h, ii) SOCl₂, reflux 2h; c) SOCl₂, EtOH, reflux 5h; d) K₂CO₃, KI, DMF, stirred 12h at 45°C; e) i) NaOH, THF, 25°C, ii) dilute HCl.

Ligand with alkyne group was synthesized firstly by the

method of scheme 2. Amphiphilic dextran Dex-g-LA/azide with aliphatic chains and azide groups grafting onto the dextran backbone was synthesized by esterification reaction between the hydroxyl group (-OH) of dextran and the carboxyl group (-COOH) of lauric acid (LA) and connect a small molecules with azide. Ligand with alkyne group was then grafted onto the surface of micelles of Dex-g-LA/azide in water. MnCl₂ • 4H₂O was added in the micelles solution to obtain the multivalent MnL decorated amphiphilic dextran micelles.

Results: Ligand with alkyne group, amphiphilic dextran Dex-g-LA/azide and multivalent ligands decorated amphiphilic dextran Dex-g-LA/L were synthesized and characterized by ¹H NMR. Multivalent MnL decorated amphiphilic micelles was prepared and characterized by SEM and DLS. T₁ relaxivity of the micelles and MnL in water was measured at 1.5 T under a clinical MR scanner (Siemens Sonata), and shown in Figure 1. Dex-g-LA/MnL micelle has a higher T₁ relaxivity of 5.6 Mn⁻¹s⁻¹ than that of MnL (4.1 Mn⁻¹s⁻¹).

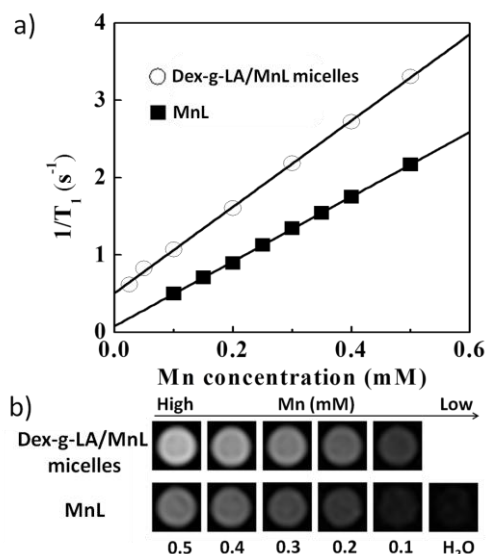


Figure 1. a) T₁ relaxation rates (1/T₁, s⁻¹) of multivalent MnL micelles and MnL as a function of Mn concentration (mM) at 1.5 T; b) T₁-weighted MRI images (1.5 T, spin echo sequence: TE = 5.3 ms, TR = 50 ms).

Conclusions: Modification of ligand and conjugation of it onto polymeric nanoparticles via rigid triazole ring of click chemistry led to the formation of multivalent ligand nanoparticles. Corresponding multivalent MnL has higher T₁ relaxivity and better sensitivity than that of free MnL.

References: 1. Pan D. *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.*, 2011;3;162-173; 2. Su H. Wu C. Ai H. *Dalton Trans.* 2012;41;14480-14483.