Paramagnetic Gd-based Gold Glyconanoparticles as MRI Contrast Agents for Brain Tumor Detection

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Nanoparticles for Magnetic Resonance Imaging (MRI) have attracted much attention in the last years.[1] Most of them consists in magnetic iron oxide nanoparticles (T_2 agents) which have some disadvantages that limit their extensive clinical applications. For example, they are negative imaging agents (signal-decreasing effect) and their high susceptibility induces distortion of the magnetic field on neighbouring normal tissues. Because of this, most extensively and clinically used MRI contrast agents are T_1 agents (signal-increasing effect) based on gadolinium complexes.[2] Many research groups are devoting their work to develop nanoparticle-based T_1 contrast agents, in which the core material is composed by Gd (III) salts.[1] Recently, the synthesis of gold nanoparticles capped with a Gd-based contrast agent (DTDTPA) has been reported.[3] Our laboratory has a great expertise in preparing gold nanoclusters and semiconductor nanocrystals functionalized with carbohydrate antigens (glyconanoparticles, GNPs).[4] These gold GNPs have been shown to be excellent platforms for basic studies of carbohydrate interactions and potential tools for biotechnological and biomedical applications. GNPs are multivalent sugar-coated gold nanoclusters. The sugar coat confers water solubility and biological activity to the nanoclusters. GNPs are biocompatible and non-toxic to cellular lines or mice,[5] thus being good candidates for in vivo use. The methodology developed in our laboratories allows us to introduce multifunctionality in a controlled way.[6]

We herein present hybrid GNPs having on the same gold nanoplatform sugar conjugates and Gd(III) chelates for converting GNPs into new paramagnetic probes for MRI. The insertion of both Gd-complex derivatives and suitable glycoconjugates in a one-step process onto the same gold nanocluster can enhance the relaxation properties of the Gd-chelate. Both sugar stereochemistry and the relative position of the sugar with respect to the Gd(III) ion seem to control the relaxivity values of these GNPs. The paramagnetic gold GNPs were prepared using different ratios of thiol-ending sugar (glucose, galactose, mannose, cellobiose, maltose or lactose) conjugates and tetraazacyclododecane triacetic acid (DO3A) ligands (Scheme 1). DO3A-ligands were selected to chelate the Gd(III) cation. Twenty hybrid GNPs were prepared by reducing a gold salt in the presence of a mixture of glycoconjugate and ~10% of $DO3AC_5S$ or $DO3AC_{11}S$, following our methodology.[7] Transmission electron microscopy (TEM), UV-Vis, IR, ^1H NMR, and elemental analysis were used for their characterization (Scheme 1). The prepared GNPs were incubated with $GdCl_3$. The amount of Gd^{3+} present in the GNPs has been measured by ICP and by UV complexometric titration (xylenol orange test). One important characteristic of these GNPs is the number of water molecules coordinated directly to the Gd(III) (q) which was measured using ^{17}O NMR resonance.

The longitudinal and transversal relaxation times (T_1 and T_2) of our GNPs were measured to confirm their potentiality as MRI contrast agents. They showed very good relaxivities values (r_1 and r_2), even better than commercial available contrast agents. Gluco-GNPs have been used as in vivo contrast agents for detection of brain tumours (GL261 brain glioma in mice) using a 7 T horizontal magnet. Commercial Dotarem® was used as reference at the same dose (0.04 mmol Gd/Kg, i.v. injection in the tail vein). Dynamic Contrast Enhanced T_1 images (DCE-T_1) and

relative contrast enhancement (RCE) are shown in Fig. 1. Gluco-GNPs reached brain tumours and accumulate there, allowing their visualization by MRI.

The promising results of the contrast enhancement observed with the evaluated GNP suggest that Gd-based GNPs could be used as new nano-probes for brain tumour detection in vivo. Besides, GNPs can be further derivatized to improve targeting.

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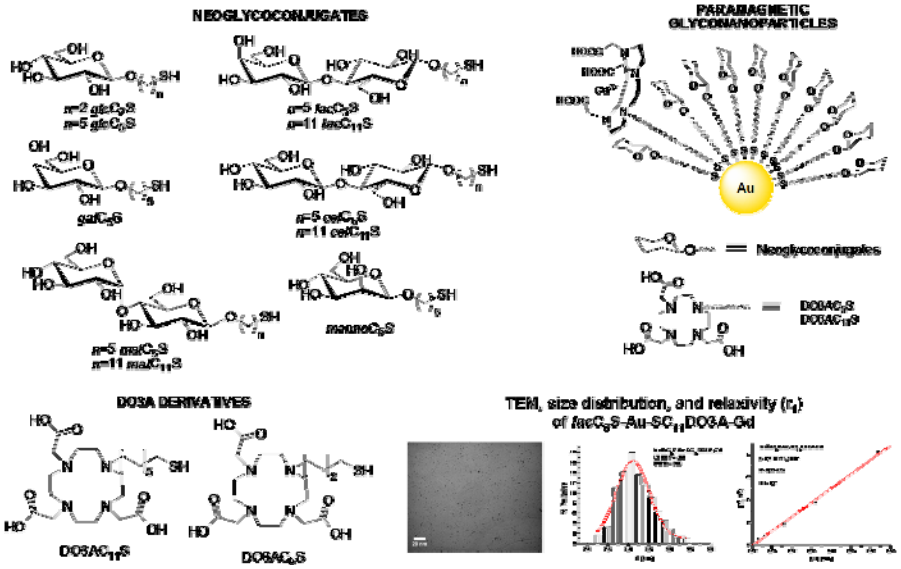
Figures:



Scheme 1

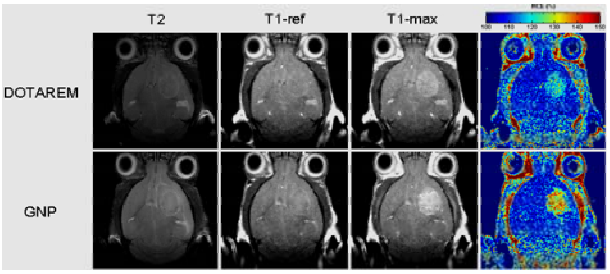


Fig. 1: Left to right, axial T2-weighted images, DCE-T1 images and RCE maps of 2 mouse brains with a GL261 glioma. One animal was studied with Dotarem (top row) and the other with the GNP (bottom row). T1-ref images were acquired before injecting the agent; T1-max images correspond to the point of maximum contrast enhancement after Dotarem or GNP administration.