GLYCONANOTECHNOLOGY: A METHOD FOR THE PREPARATION OF BIOFUNCTIONAL NANOPARTICLES WITH APPLICATION IN NANOMEDICINE

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Our laboratory has developed an integrated strategy to study and intervene in carbohydrate-mediated interactions, named Glyconanotechnology [1,2,3]. It allows the preparation, in a simple way, of a great variety of sugar functionalized self assembled monolayers on 3D-gold nanoclusters (Glyconanoparticles, GNPs) [3,4]. The biofunctional GNPs are water soluble, globular shaped and with well defined composition. They present in a multivalent way the ligands, thus constituting a good biomimetic model of carbohydrate presentation at cell surface. The preparation of multifunctional GNPs incorporating, in a control manner, not only carbohydrates, but also a selected set of ligands (DNA, RNA, peptides, fluorescent probes, etc) on the same cluster is comprised within the potential of this technology. These tools allow us to intervene in cell adhesion and recognition processes.

Based on this technology, three main projects are being developed in our laboratory:
- GNPs as microbicides against HIV infection
- Magnetic GNPs as contrast agents in Magnetic Resonance Imaging (MRI)
- GNPs as non-viral transfection agents

This lecture will focus on the presentation of our results and applications of GNPs as potential microbicides for blocking HIV-1 infection and as contrast agents in MRI for brain tumor targeting.

One of the mechanisms of HIV vaginal infection is mediated by the interaction between the envelope glycoprotein gp120 of the HIV-1 and the DC-SIGN receptor of dendritic cells [5]. DC-SIGN recognizes high-mannose oligosaccharides which are present in the glycoprotein gp120. GNPs capped with the mannose structural motives present in the gp120 were prepared and tested by Surface Plasmon Resonance (SPR) as inhibitors of the binding of DC-SIGN to gp120. Free oligomannosides need millimolar concentrations to give 100% inhibition; mannose GNPs increase effectiveness requiring micromoles concentrations. The best inhibitor, with an effective concentration at nanomolar scale, was a GNP capped with the disaccharide Manα1-2ManαGNP (Figure 1). The evaluation of this inhibition *in vitro* with cell based models and the effect in dissemination of HIV-1 from cells bearing DC-SIGN to T-cell populations will be also illustrated.

Gd(III) chelates are in use in medical diagnostic as MRI contrast agents [6]. The construction of novel paramagnetic GNPs functionalised with different sugars (glucose, lactose, galactose) and containing Gd(III) complexes of a DOTA derivative (in ~ 10% proportion) was achieved. Aliphatic linkers of different lengths (two, five or eleven carbon atoms) were used to study the influence of the presentation and rigidity on the relaxivity of the system. Relaxation times T_1 and T_2 were measured with a Minispec at 1.5 T to calculate r_1 and r_2 relaxivity values. Phantoms containing solutions of the compounds were also imaged at 7.0 T. *In vivo* imaging of intracerebral glioma in mice was run and the images were compared with the ones obtained with commercial Magnevist® (gadolinium DTPA) (Figure 2).

Details on the synthesis, characterization, cytotoxicity of the GNPs will be also given.

References:

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Figures:

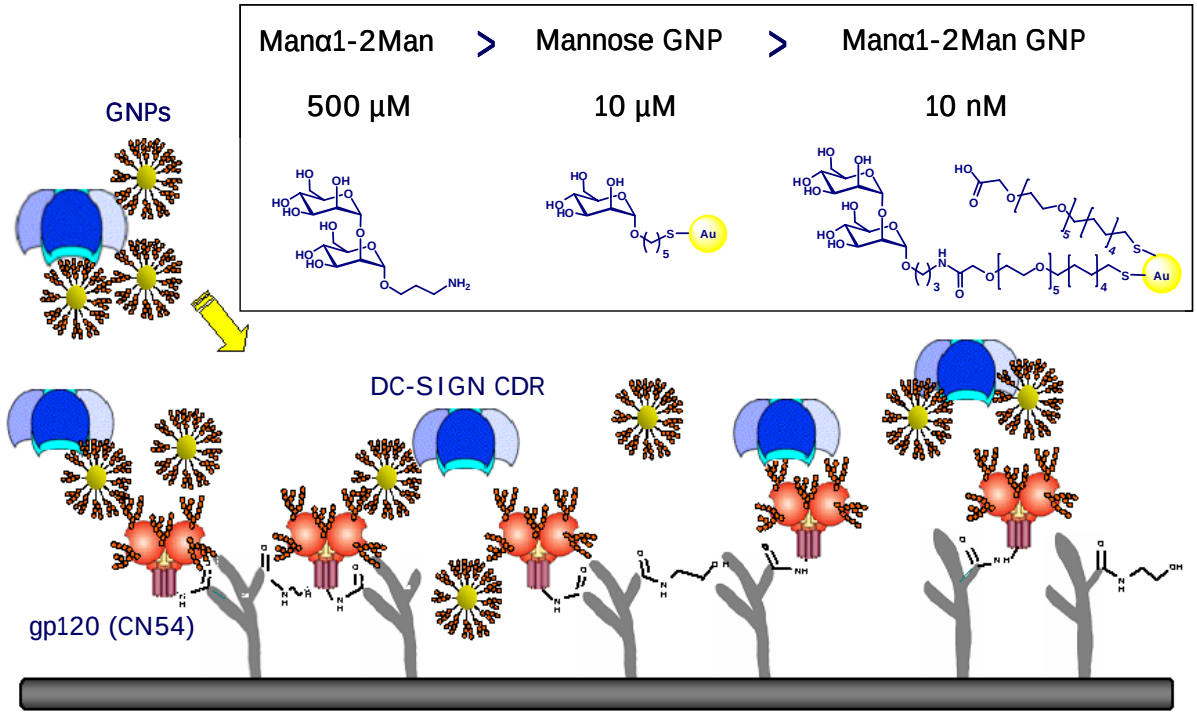

Figure 1. Dose dependent inhibition of GNPs on the binding of DC-SIGN to gp120 as measured in a BIACORE (DC-SIGN and GNPs fluid phase over immobilized gp120 on surface)

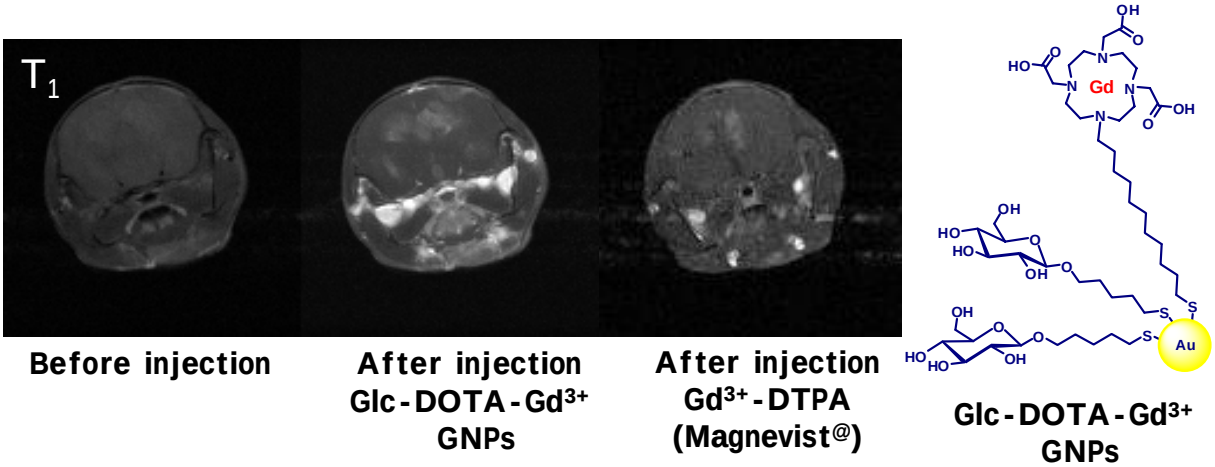

Figure 2. Precontrast and postcontrast T_1-weighted images of intracerebral glioma in mice: comparison between Glc-DOTA-Gd^{3+} GNPs and Magnevist® (in collaboration with IIB "Alberto Sols" of Madrid)