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"Development of new bimodal imaging agents based on Mn(II)"

ABSTRACT

The combination of the great spatial resolution of Magnetic Resonance Imaging techniques (MRI) with the high sensitivity of Positron Emission Tomography (PET) is a very attractive perspective. To fulfil this purpose, bimodal imaging agents are required. Complexes containing transition metals or lanthanides are the most studied ones. Mn(II) seems to be an ideal metal ion for this purpose. Having five unpaired electrons (S = 5/2 in the high-spin state), slow longitudinal electronic relaxation and a fast H_2O exchange rate, Mn(II) is a promising candidate for MRI (especially T_1-based MRI) and represent a safer alternative in comparison to Gd(III), which use has been recently associated to nephrogenic systemic fibrosis.[1] Moreover, similarly to essential metal ions, small Mn(II) excess can be easily excreted by the organism, avoiding its accumulation in bones and tissue. ^{52}Mn represents an interesting long-lived PET radionuclide ($t_{1/2}$ = 5.6 days) with a β^+ emission of 575 MeV (29% yield).[2] Despite these very interesting properties, Mn(II)-based imaging agents are not very diffused and the major part of the studies is focused on the use of Mn(II) for MRI applications. The main issue in developing new chelators for Mn(II) complexes is the difficulty to obtain metal complexes showing both thermodynamic stability and kinetic inertness. This is mainly due to the lack of LFSE for Mn(II) d^5 (high spin state) and its low positive charge. Kinetic inertness is a pillar factor for *in vivo* applications, in fact the release of Mn(II) as consequence of trans-metallation and trans-chelation processes must be strictly controlled. The best results in Mn(II) complexation were obtained using macrocyclic chelators: 2,2′,2″,2‴-(1,4,7,10-tetraazacyclododecane-1,4,7,10-tetrayl)tetraacetic acid (DOTA) derivatives. Moreover, some acyclic ligands have shown interesting complexation properties for Mn(II), for instance cyclohexanediaminetetraacetic acid (CDTA) and its derivatives.[3]

The aim of my PhD project is to synthetize new chelators (L) capable to form metal complexes with Mn(II) in 1:1 metal-to-ligand molar ratio **[Mn(II)L]** characterized by thermodynamic stability and kinetic inertness in physiological conditions. The first part of the project will be focused on the synthesis of the new chelators and their full characterization. The complexes [**Mn(II)L**] will be prepared and characterized by thermodynamic measurements (spectrophotometric and potentiometric) and pharmacokinetic studies (dissociation rate, trans-metallation and trans-chelation experiments). The radiolabelling with ^{52}Mn will be planned and the labelling conditions optimized. The chelators will be then functionalized to provide bifunctional chelators (BFCs), these are obtained by grafting two different moieties: the metal chelating site (chelator) and a reactive functional group able to form a chemical bond with a specific targeting vector (**Tv**). The last part of the project will consist in the binding of the BFC to a model targeting vector **Tv** and subsequent Mn(II) complexation, to obtain a system of general formula **[Mn(II)LTv]** (**Figure 1**). Radiolabeling with ^{52}Mn will be set up and pharmacokinetics will be carried out.

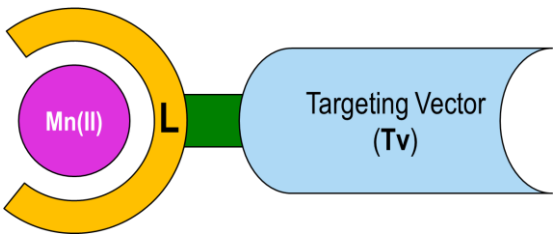

Figure 1: schematic representation of the system [Mn(II)LTv].

REFERENCES

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