**Improvement of pyclen-based manganese complexes relaxivity by using polymer vesicles (polymersomes)**

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**Introduction**

Magnetic resonance imaging (MRI) is a powerful technique due to its high resolution. Its low sensitivity can be relieved by a contrast agent, but the commercial contrast agents are gadolinium complexes which can lead to NSF disease.1 That is why the synthesis of complexes based on another cation, like manganese2, is interesting because they are potentially less toxic. To increase their efficacy, their incorporation into a polymersome is envisaged to increase the rotational correlation time τR. A fluorescent probe will also be incorporated to obtain a bimodal system active in optical imaging.

**Methods**

The pyclen macrocycle is obtained by a macrocyclization between an upper part and a lower part appropriately functionalized to allow selective deprotection steps, as well as the presence of a limited number of coordinating atoms. An arm present on the pyridine moiety allows the functionalization of the molecule. The final product is obtained by some deprotection reactions followed by a coupling reaction on the arm and finally the deprotection of -tBu groups to complex the ligand with manganese ions.3

The polymer vesicles also called polymersomes, composed of a pH sensible diblock PEO-b-PCL, are obtained by the nanoprecipitation route in the presence in the aqueous phase of ZW800-1, an indocyanine green derivative. (Figure 1) They are then purified by size exclusion chromatography.

**Results/Discussion**

Each intermediate were completely characterized by NMR and mass spectrometry to attest their structure. The obtained pyclen based manganese complexes were then fully characterized by relaxometry to evidence their efficacy. The presence of one fast exchanging water molecule in the inner coordination sphere of the metal cation was evidenced by 17O NMR. Their NMRD profiles were then recorded and fitted with the Solomon and Bloembergen model. This has allowed to show a slight increase of the relaxivity when the arm is present on the pyridine moiety due to a slight increase of τR.3

Polymersomes were prepared in different conditions by varying the hydrophobic block length of the copolymer. They were then characterized by DLS and MALS in order to obtain both their hydrodynamic and gyration radii and demonstrate their structure. The rate of encapsulation of the fluorescent probe was also determined by fluorescence spectroscopy to optimize it and to perform model drug release experiments.

**Conclusions**

The pyclen derivatives complexed with manganese cations were obtained and fully characterized. Their T1relaxivities are close to that of the Dotarem® commercial MR contrast agent. Fluorescent polymersomes active in optical imaging were also obtained and characterized. In a near future, the manganese complexes will be incorporated in the polymersomes to increase their efficacy and obtain a bimodal probe active in both MRI and optical imaging.

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**Disclosure**

I or one of my co-authors have no financial interest or relationship to disclose regarding the subject matter of this presentation.

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