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Multiple Myeloma *in vivo* imaging with Bispidine Antibody-conjugates

Supervised by:

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Context: Multiple myeloma (MM) is a malignant disease of the bone marrow that induces the uncontrolled proliferation of abnormal plasma cells. MM is not curable and develops into a chronic disease requiring repeated treatment. In order to improve patients' management, it is essential to develop new molecular imaging tools with high specificity and very good sensitivity (down to pM). We will focus on Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) which are two complementary imaging techniques in terms of sensitivity and spatial resolution. For each of these two techniques, a metal ion (Mn for MRI or a radioisotope for PET) plays the main role of "reporter" and induces the signal. However, in both cases, the ions must be chelated and form complexes resistant to *in vivo* dissociation.

The particularity of the bispidine ligands (3,7-diazabicyclo[3.3.1]nonane) lies in their rigid and pre-organised backbone, which allows rapid complexation kinetics of 64-Cu under high dilution conditions suitable for PET, and a high kinetic inertia of the complexes favourable to their application *in vivo*.[1,2] For MRI, the technology developed by the SynPA team is based on the use of Mn^{2+}.[3] These complexes have a similar efficacy or even superior to commercial Gd^{3+} complexes, while presenting a more important safety profile.

Objective: The PhD student will synthesize a library of new chelates based on the bispidine skeleton and adapted to the complexation of 64-Cu and 55-Mn. Their complexation with the different metals will be characterised by usual physico-chemical techniques and, in the case of 64-Cu, radiochemistry. The chelates will be conjugated with antibodies of interest (anti-BCMA, anti-CD38) and characterised by high resolution mass spectrometry (coll. Sarah Cianférani, LSMBO, IPHC). Affinity and toxicity measurements (*in vitro*) of the immunoconjugates and their complexes will be performed at ICANS. Radiolabelling with 64-Cu, in vitro and in vivo imaging will be carried out on xenografted mouse models at the Nantes Angers Cancer and Immunology Research Centre (CRCINA), in collaboration with the teams of Prof. Michel Cherel and Prof. Yannick Guillou.

Expected skills: Multi-stage organic synthesis and standard characterization techniques; Skills and a taste for coordination and physical chemistry; English; Energy, rigour, method and tenacity.

Application/further information: Email us at aline.nonat@unistra.fr and a.detappe@icans.eu (before July 18th, 2022).

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