PhD course in Models and Methods for Material and Environmental Sciences – XXXIX cycle

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"Lead-212 and Titanium-45 as emerging isotopes for radiopharmaceutical applications: production and development of new bifunctional chelators"

Radiometals are radioactive isotopes used in diagnostics and therapy. To apply them for specific medical purposes, chelators are essential to tightly bind them. Typically, bifunctional chelators (BFCs) are employed for their ability to complex with the metal and to link with biologically active targeting molecules. The choice of radiometal is critical, as it determines the therapeutic or diagnostic properties. Diagnostic radiometals emit photons that minimally interact with biological tissues (e.g., γ rays or annihilation photons produced by positron (b^+) decay), while therapeutic radiometals emit radiations that highly interact with the surrounding environment exerting a local toxic effect (e.g., □ or a particles)[1]. One promising therapeutic radionuclide is Lead-212 ($t_{1/2}$ = 10.6h), that has a decay chain resulting in the release of multiple therapeutic particles and, in particular, it decays to Bismuth-212, that can be used as an *in-situ* generator for α particles. The interest in Lead-212 is further driven by another lead isotope, Lead-203 ($t_{1/2}$ = 51.9h), ideal for SPECT imaging. The combination of these two lead isotopes forms a theranostics pair, an emerging concept in this field [2]. Another emerging radioisotope is Titanium-45 ($t_{1/2}$ = 3.1 h), a β^+ emitter suitable for PET imaging[3].

Selecting the right chelator is crucial for securing the metal for safe biological transport. Limited examples are reported on titanium-45 complexes due to its underdeveloped radiochemistry[3], while research on lead chelators has mainly focused on azamacrocyclic ligands like 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA) and its derivative TCMC (1,4,7,10-tetrakis(carbamoylmethyl)-1,4,7,10-tetraazacyclododecane)[4]. Nonetheless, there is a growing interest in alternative ligands, as non-macrocyclic, that can address the stringent demands of metal chelation in nuclear medicine.

My PhD project aims to develop new bifunctional chelators for the complexation of these new emerging radiometals. The initial phase will imply the synthesis of new chelators and their full characterization through thermodynamic measurements, including spectrophotometric and NMR spectroscopy, and pharmacokinetic studies such as dissociation rate, transmetallation and transchelation experiments. The radiolabeling will follow this first "cold" investigation. The first step will be focused on the radionuclide production, especially the optimization of the production route to achieve high radionuclidic purity. Subsequently, radiolabeling with lead-212 and titanium-45 will be planned, with a focus on defining the optimized labeling conditions. Finally, the chelator will be further functionalized to provide the desired bifunctional chelator, that will be coupled with different targets. The radiochemical part will be carried out at the Institute of Nuclear Chemistry of Johannes Gutenberg-University Mainz (DE) under the supervision of Prof. Patrick Riß.

References:

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