PhD position (CIFRE): Development of a new generation of radiopharmaceuticals for alpha targeted radionuclide therapy of cancers

Keywords:
Therapeutic innovation - personalized medicine – targeted radionuclide therapy – radiopharmaceuticals – pre-targeting - multidisciplinarity

Context:
Targeted radionuclide therapy (TRT) is becoming increasingly important in the therapeutic arsenal to fight cancer. This strategy consists of delivering a radionuclide to tumor cells to kill them. This radionuclide can be a β- emitter (^{177}Lu, ^{90}Y), a α emitter (^{225}Ac, ^{223}Ra, ^{212}Pb/^{212}Bi) or Auger electrons (^{161}Tb, ^{111}In). The latter must be linked to a targeting vector which will specifically target receptors overexpressed on the surface of cancer cells and/or the tumor microenvironment. The targeting molecule may be a monoclonal antibody or an antibody fragment, a peptide or a small ligand. Since most of the radioisotopes used for TRT are metallic elements, it is necessary to conjugate to the vector a chelating agent designed to form a stable complex with the metal ion. Although this strategy has been explored for several decades, it has witnessed an extremely rapid development in recent years with the FDA approval of two compounds: Lutathera® in 2018 and Pluvicto® in 2022, for the treatment of neuroendocrine tumors and metastatic castration-resistant prostate cancer (mCRPC), respectively. The efficacy of a radiopharmaceutical for TRT depends on a large number of factors (nature of the target and the targeting vector, of the radionuclide and the chelating agent, of the linker between the chelating agent and the vector) often interdependent on each other, which makes the optimization of the compound tricky.

Project:
The objective of this CIFRE thesis is to develop, in partnership between a biopharmaceutical company and the Institut de Chimie Moléculaire de l'Université de Bourgogne à Dijon, a new generation of radiopharmaceuticals for TRT, by optimizing the different components of the radiopharmaceutical and their combination for optimal therapeutic efficacy, while limiting the side effects of TRT. Several innovative strategies will be explored: i) optimization of the radioconjugate format, ii) pre-targeting approaches, iii) original strategies in chemistry. Based on innovative vectors provided by the industrial partner and the continuous support of the teams (multi-disciplinary project), the project will require the synthesis of some of the biovectors to be evaluated, the development of radiolabeling protocols (^{225}Ac and ^{177}Lu), the evaluation of radioconjugates in vitro, and in vivo, in healthy animals in order to determine their pharmacokinetics. Finally, the therapeutic efficacy of the radioconjugates presenting the most favorable pharmacokinetics will be evaluated in animal models with subcutaneous tumors developed by the industrial partner.

Candidate profile:
Master's degree (or equivalent) in chemistry/biochemistry. We are looking for a highly motivated candidate interested in a particularly interdisciplinary subject, at the chemistry – biology – radiopharmacy interface. Knowledge in radiochemistry and cell biology will be appreciated.

Contact: Send a CV (with 2-3 references) and a cover letter to Prof. Franck Denat, franck.denat@u-bourgogne.fr