Université de Bretagne Occidentale
UMR CNRS 6521: *"Chimie, Electrochimie Moléculaires et Chimie Analytique"*

Post-Doctoral Position in Chemistry
18 months (ANR Funding)

Azamacrocyclic synthesis for new copper PET-imaging radiotracers

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Abstract of the project

Tetraazamacrocycles, such as cyclam are renowned as efficient chelating agents for numerous metal ions. Owing to the presence of secondary amine functions, these macrocycles can be N-functionalized with various coordinating groups, which allows the preparation of a wide range of ligands suitable for many applications such as molecular recognition, catalysis, purification of liquids, and the development of metal-based imaging and therapeutic agents in medicine.

Copper complexation is currently attracting a huge amount of research interest owing to the importance of the complexes of Cu^{2+} in numerous fields, such as the preparation of biomimetic complexes, cation detection and sensing, or the development of metal-based imaging and therapeutic agents. Indeed, significant progress has been achieved in the past years in nuclear medicine to find stable chelates of radioactive copper ions, particularly ^{64}Cu. The use of this radioisotope for PET (Positron Emission Tomography) imaging requires the development of specific ligands able to form highly stable complexes with the radioactive metal ion to avoid its transchelation in biological media. Therefore, Cu^{2+} complexes which can be used as radiopharmaceuticals must be thermodynamically stable and kinetically inert in highly competitive or even reductive, biological media. Besides, considering the relatively rapid decay properties of ^{64}Cu (12.7 h), the complex formation must be fast enough to avoid significant activity losses before administration of the radiopharmaceutical.

Among the vast range of acyclic and cyclic ligands that have been successfully used for copper(II) complexation, the family of tetraazamacrocycles with N-appended coordinating arms stands out for the efficiency and versatility of their copper chelation. To improve the efficiency of radiopharmaceuticals, it is useful to append a targeting biomolecule on the chelating moiety to induce site-specific delivery of the radiation, producing a bifunctional chelator (BFC). Obtaining a BFC requires the introduction of an appropriate conjugation group into the structure of the metal chelator, which allows for bioconjugation before or after labeling with the radioisotope.

In our objective to develop more efficient copper chelators such as **DOTA** or **NOTA**, already under study but with several drawbacks, azamacrocycle ligands with picolinate functionality were investigated by our group. Among them, **TE1PA**, a monopicolinate cyclam, was proven to have interesting properties with fast kinetics, high thermodynamic stability, Cu(II) selectivity, and inertness even in the Cu(I) state, especially compared to the azamacrocycles mentioned above. The usefulness of ^{64}Cu-TE1PA in an *in vivo* animal model has already been demonstrated. Following these results, we recently synthesized a new C-functionalized derivative of TE1PA: the p-SCN-Bn-**TE1PA**. This compound, functionalized in a similar design as the commercially available BFC p-SCN-Bn-**DOTA** or p-SCN-Bn-**NOTA**, was synthesized in order to allow a high conjugation efficiency between the chelator and antibodies, and a proof of concept was established in a syngeneic multiple myeloma model.

We have very recently investigated the possibility of applying our chelator for the development of ^{64}Cu-PET radiopharmaceuticals for venous thrombosis. Venous thromboembolism (VTE), clinically presenting as deep vein thrombosis (DVT) or pulmonary embolism (PE), is an important health issue. As VTE is the third most frequent acute cardiovascular syndrome behind myocardial infarction and stroke and is strained with high mortality, public health agencies have highlighted the importance of stimulating research in VTE. ^{64}Cu seems to be the most suitable radionuclide for PET imaging of venous clot due to advantageous decay characteristics allowing late acquisition and thus satisfactory tissue to background contrast in case of tracers with low clearance from blood. Knowing the advantages of our ^{64}Cu chelator, the goal of this project is to develop in a very large consortium, new radiotracers (^{64}Cu-TE1PA-antibody, -peptide or -protein) and test them in pre-clinical models of VTE. We hypothesize that these three new PET tracers will improve recurrent VTE diagnosis and patient management avoiding inadequate treatment in patients with residual clots.

Postdoctoral

Postdoctoral works: The work takes place at the very beginning of the program. The recruited post-doctor will be in charge of the synthesis of polyazamacrocyclic derivatives able to strongly coordinate ^{64}Cu (in terms of thermodynamic and inertness). Bifunctional TE1PA chelators (with different conjugation functions) will be considered as well as the study of their conjugation on various biomolecules (peptides, proteins and antibodies). The bifunctionality is essential to ensure both the strong complexation of the radioelement and the grafting on the biovector.

Position profile: The young researcher, localized in CEMCA Laboratory (UMR 6521) will have a serious background in organic chemistry (and if possible in macrocyclic chemistry). A good knowledge in bioconjugation reactions (click chemistry, NHS, maleimide…) as well as an expertise in purification by HPLC will also be important additional assets. The post-doc will also have an affinity for bio-applications and will frequently interact with the different partners of the project (INSERM Brest and Nantes / Nantes Nuclear Medicine Centre). A short mission in these different group-partners is expected for the bioconjugates synthesis and characterization, as well as for the first radiolabelling experiments.

Researched profile: We are looking for a motivated and experienced candidate in organic synthesis with a strong openness to coordination chemistry and health applications, particularly in imaging / nuclear medicine. Although a large part of the work will be in organic synthesis, the post-doctoral fellow will work in interaction with our collaborators for the applications part (biology and radiolabelling); for this part, no specific skills are required.

References:

. Synthesis of a C-functionalized TE1PA and comparison with analogues. Example of bioconjugation on 9E7.4 mAb for multiple myeloma ^{64}Cu-PET imaging. T. Le Bihan, A.-S. Navarro, N. Le Bris, P. Le Saëc, S. Gouard, F. Haddad, J.-F. Gestin, M. Chérel,A. Faivre-Chauvet and R. Tripier, *Org. Biomol. Chem.,* **2018**, 16, 4261-4271.

. TE1PA as innovating chelator for ^{64}Cu immuno-PET imaging: a comparative *in vivo* study with DOTA/NOTA by conjugation on 9E.7.4 mAb in a syngeneic multiple myeloma model. A.-S. Navarro, T. Le Bihan, P. Le Saëc, N. Le Bris, C. Bailly, C. Saï-Maurel,J.-F. Gestin, M. Chérel, R. Tripier and A. Faivre-Chauvet, *Bioconjugate Chemistry*, **2019**, 30, 9, 2393-2403.

. *In Vivo* Albumin-Binding of a C-Functionalized Cyclam Platform for ^{64}Cu-PET/CT Imaging in Breast Cancer Model, T. Le Bihan, C. H. S. Driver, T. Ebenhan, N. Le Bris, J. R. Zeevaart and R. Tripier, *Chem. Med. Chem.*, **2021**, 6(5):809-821.

Application before 15 / 11 / 2021:
CV, cover letter and 2 recommendations must be sent to:

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Starting: 01/01/2022
Salary: 2665 euros (before taxes)