Open thesis position 2023 in
organic/coordination/radiopharmaceutical chemistry:

Design and evaluation of ligands for the complexation of astatine-211

Background:

This thesis offer is part of the SAt-Radio project, funded by the European Research Council (ERC) from 1 October 2023. Astatine-211 is an alpha-emitting radioisotope with a 7.2-hour half-life that holds great promise for cancer therapy. Associated with a specific vector molecule of a type of tumor cell, astatine-211 can be transported as close as possible to tumor sites to deliver its high-energy radioactive radiation, allowing the destruction of targeted cells. Astatine-211 can be artificially produced using a particle accelerator. In particular, the Arronax cyclotron located in Nantes (France) is one of the most powerful accelerators in the world allowing its production. It is expected to enable clinical applications of astatine-211 in various cancer pathologies in the coming years. In order to produce an astatine-211-based radiopharmaceutical, chemical synthesis steps are required. As astatine is the heaviest of halogens, synthetic approaches typical of halogens are most often implemented with the formation of astatine-carbon bonds. However, this type of bonding is most often found to be insufficiently stable *in vivo*, and astatine dissociates from its vector before reaching its tumor target, leading to unwanted irradiation of healthy tissues. It is therefore necessary to find alternatives to the astatine-carbon bond. Astatine is the rarest chemical element on Earth, so it has been studied very little and the possibilities of new developments are numerous.

Hypotheses and research program of the thesis:

Although belonging to the halogen series, astatine exhibits characteristics of metals due to the relativistic effects observed for heavy elements (Z = 85). Several studies have shown this metallic character and the ability of some oxidized species of astatine to form complexes with various ligands. However, no complex sufficiently stable for *in vivo* use has been reported to date.

Thus, this thesis project aims to exploit the metallic character of astatine for the design of radiopharmaceuticals by drawing on the tools recently developed by the team and its partners to design astatine chelating agents in a rational way.

A first phase of the project will be the synthesis and evaluation of simple model ligands, in order to determine which will be the most suitable to be assembled in pre-organized polydentate ligands. This work will be carried out with the support of molecular modelling carried out by Dr. Nicolas Galland

CRCI²NA
Centre de Recherche en Cancérologie
et Immunologie Intégrée, Nantes Angers

François Guérard
Research Scientist

francois.guerard@univ-nantes.fr
Team 2 Nuclear Oncology

(CEISAM laboratory, Nantes) to compensate for the small amount of astatine involved in experimental studies that limit the use of conventional spectroscopic tools. A thermodynamic stability study will be carried out with the support of Gilles Montavon (Subatech laboratory, Nantes).

In a second phase of the study, the most promising chelating agents will be functionalized for coupling to vector molecules such as peptides or antibodies targeting the cancers studied in the team. This will allow the evaluation of the radiopharmaceuticals thus produced, in particular their stability in the biological environment compared to the radiolabelling methods currently described as insufficiently stable.

Candidate Profile:

The candidate will have obtained his master's degree in chemistry in 2022 or 2023. Very good skills and experience in organic synthesis are essential. Good training in coordination chemistry is an asset. No radiochemistry experience required. Good communication skills are required to interact with the partners associated with this multidisciplinary project.

Application:

Candidates will send a CV and a cover letter as well as the names of two referees to francois.guerard@univ-nantes.fr

Références in relation with the project:

1. Guérard, F., Maingueneau, C., Liu, L., Eychenne, R., Gestin, J.-F., Montavon, G. & Galland, N. Advances in the Chemistry of Astatine and Implications for the Development of Radiopharmaceuticals. Acc. Chem. Res. 54, 3264–3275 (2021).
2. Berdal, M., Gouard, S., Eychenne, R., Marionneau-Lambot, S., Croyal, M., Faivre-Chauvet, A., Chérel, M., Gaschet, J., Gestin, J.-F. & Guérard, F. Investigation on the reactivity of nucleophilic radiohalogens with arylboronic acids in water: access to an efficient single-step method for the radioiodination and astatination of antibodies. Chem. Sci. 12, 1458–1468 (2021).
3. Maingueneau, C., Berdal, M., Eychenne, R., Gaschet, J., Chérel, M., Gestin, J.-F. & Guérard, F. 211At and 125I-Labeling of (Hetero)Aryliodonium Ylides: Astatine Wins Again. Chem. Eur. J. 28, e202104169 (2022).