	Nom du Laboratoire d'accueil **:** **Laboratoire de Chimie de Coordination du CNRS** Directeur : **Azzedine BOUSSEKSOU** Site web du laboratoire et/ou de l'équipe d'accueil **:** **https://www.lcc-toulouse.fr/** Nom du groupe de recherche qui accueille l'étudiant(e) **:** **Alzheimer, Amyloids and Bioinorganic Chemistry (ALAMBIC) https://hureaulab.wixsite.com/equipeflcc** Nom du responsable de stage **: Emilie MATHIEU** Tél. : **05 61 33 31 20** E-MAIL **: emilie.mathieu@lcc-toulouse.fr**	**Financement MESR (en cours de demande)**

Design of lanthano-peptides as mimics of lanthanide methanol dehydrogenases

Lanthanides (Ln) have recently joined the family of elements essential to living organisms with the discovery of methylotrophic bacteria whose growth depends on their ability to produce a Ln(III) enzyme, the lanthanide methanol dehydrogenase (Ln-MDH) [1]. Ln-MDH is the sole lanthanide enzyme known to date, making it a system of fundamental interest. It contains in its active site a Ln(III) cation and an organic cofactor, the pyrroloquinoline quinone or PQQ. The activity of Ln-MDH is strongly dependent on the lanthanide present in its active site. This unexpected observation is central to the interest in Ln-MDH [1]. It is impossible to understand this selectivity by working directly with purified Ln-MDH from bacterial cultures, as these do not grow in the presence of the heaviest lanthanides (Tb-Lu) and therefore do not allow to obtain the corresponding Ln-MDH. An alternative strategy could consist in the design and synthesis of artificial enzymes [2] mimicking the structure of the active site and the activity of Ln-MDH.

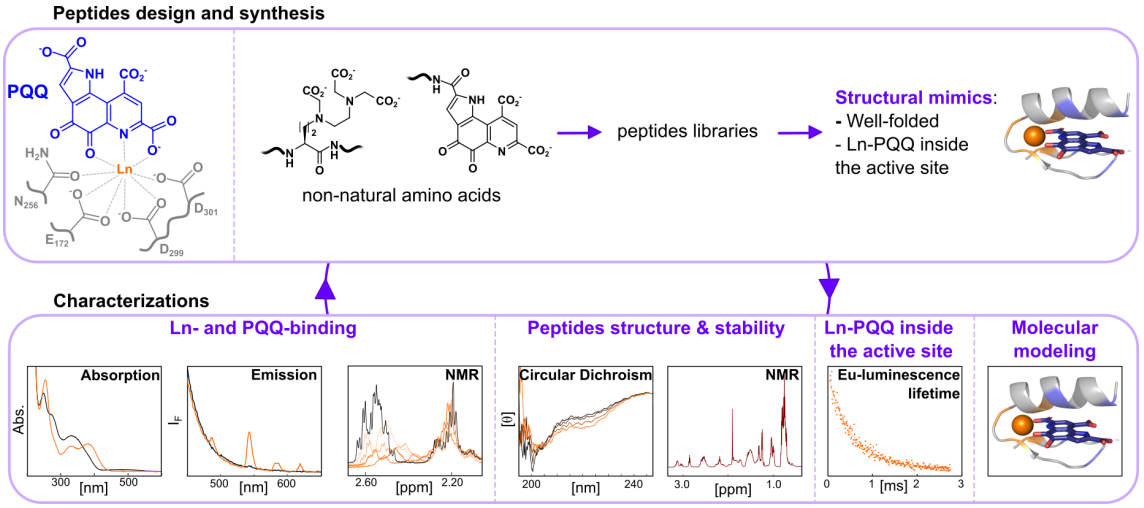
Within the ALAMBIC team, one of the ongoing research projects is the design of lanthano-peptides [3] as Ln-MDH mimics. The use of peptides is advantageous because it combines the advantages of small molecules (synthetic, modularity of their structure) and enzymes (control of the 1st and 2nd coordination spheres, fine tuning of the reactivity). The main challenge of this project is the control of the insertion of the Ln-MDH cofactors (i.e. PQQ and a Ln^{3+}) into the active site created by the folding of the peptide.

The objectives of this project are therefore to design and synthesize peptides with a well-defined fold that contain both Ln-MDH cofactors and that mimic the structure of the Ln-MDH active site. This represents a key first step towards obtaining functional mimics of the enzyme as tools for understanding the role of Ln^{3+} in the catalytic reaction.

To achieve these objectives, this thesis project will be divided into two parts (Figure).

The first part will be devoted to the synthesis of two peptide libraries having either a high affinity for Ln^{3+} or containing covalently bound PQQ. These two libraries will allow to determine the parameters controlling the insertion of PQQ in the active site. To obtain these peptides, non-natural amino acids will be synthesized.

A second part will be devoted to (i) the characterization of the structure and stability of the peptide-Ln-PQQ assemblies (NMR, circular dichroism, in silico modelling), (ii) the determination of the capacity of the peptides to bind Ln^{3+} ions and/or PQQ (fluorescence, UV-vis, NMR) Thanks to this information and in an iterative approach, new libraries of optimized peptides will be designed and will allow to obtain structural mimics of Ln-MDH.



The successful candidate will work in an exciting and dynamic environment at the Laboratoire de Chimie de Coordination. The technical and scientific environments in Toulouse and in the host team are of high quality and fully appropriate for the realisation of the project. The successful candidate will be trained on advanced spectroscopic techniques such as (paramagnetic) NMR, steady-state and time-resolved emission spectroscopies, and circular dichroism.

We are seeking a highly motivated student with a background in molecular chemistry and excellent grades. Applicants should have a strong interest for multidisciplinary projects in the field of bio-inorganic chemistry. Experience in organic synthesis and/or spectroscopy would be an added value. In addition, ability to write a scientific report, and strong team skills are needed.

References

[1] a. Daumann, L. J. (2019) *Angew. Chem. Int. Ed.* **2019**, *58* (37), 12795-12802; **b.** Cotruvo, J. A. (2019) *ACS Cent. Sci.* **2019**, *5* (9), 1496–1506

[2] a. Koebke, K. J. et al. (2022) *Chem. Rev.* **2022**, *122* (14), 12046–12109; **b.** Schwizer, F. et al. (2018) *Chem. Rev.* **2018**, *118* (1), 142–231

[3] a. Am Ende, C. W. et al. (2010) *ChemBioChem* **2010**, *11* (12), 1738–1747; **b.** Slope, L. N. et al. (2021) *Angew. Chem. Int. Ed.* **2021**, *60* (46), 24473–24477