

« *Laboratoire de Chimie de Coordination* » CNRS – Director : *Azzedine Bousseksou* –website : <https://www.lcc-toulouse.fr>

Team F « *Alzheimer, amyloids and bio inorganic chemistry* » team leader: Dr. C. Hureau, <https://hureauulab.wixsite.com/equipeflcc>

To apply you have to send a CV, a cover letter and your school grades (master) to the following mail address (charlene.esmieu@lcc-toulouse.fr) AND apply online through the doctoral school website <http://www.edsdm.ups-tlse.fr/> in “SDM Ph.D proposals”.

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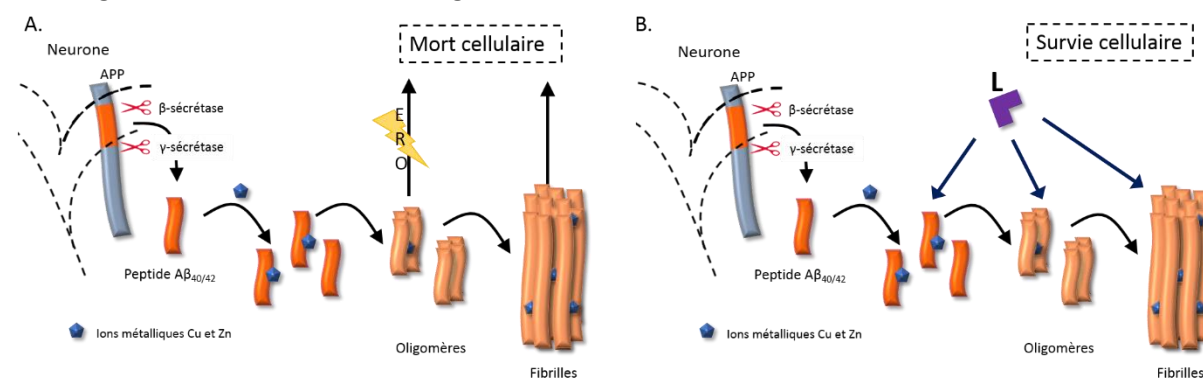
Synthesis and evaluation of fluorescent copper's ligands for the therapy by chelation in the context of Alzheimer's disease

Alzheimer's disease (AD) is the world's leading cause of dementia, and there is still no cure. In this context, it is urgent to develop new tools to help design effective drug candidates.

Although the mechanisms underlying this complex pathology are not fully understood, a consensus attributes the development of AD to the amyloid cascade. This process relies on the production of a peptide called β -amyloid ($A\beta$) and its accumulation leading to the extracellular formation of oligomers, fibrils and plaques. Such aggregates would trigger various pathological events linked to AD.

In addition, deregulation of metal ion homeostasis, particularly for copper and zinc ions, is also linked to the amyloid cascade process. Extensive evidences have associated the high toxicity of $A\beta$ -bound Cu with its ability to promote the oxidative stress observed in AD via the catalytic production of toxic reactive oxygen species (ROS). For these reasons, Cu is considered as a target of therapeutic interest. Removal of Cu from the Cu- $A\beta$ complex by ligands (L) is a particularly promising approach as it combines the advantages of impacting both (i) ROS production and (ii) toxic aggregate formation [2, 3].

It is in this context that the proposed thesis topic falls. Very promising ligands, i.e. capable of removing copper from Cu- $A\beta$ and stopping the associated ROS production, have recently been synthesized within the team [4]. Further studies are now required to better understand the parameters that enable these ligands to be effective. These ligands will also be modified to make them fluorescent.



The work of the candidate aims to improve the ligand synthesis (L), to synthesize new ligands, to synthesize their fluorescent analogues and to characterize their properties. The proposed project includes an organic synthesis phase to prepare the ligands, a physico-chemical characterization phase for the metal complexes (Cu and Zn) formed from these ligands, a study of the ligands' ability to extract Cu from Cu- $A\beta$, and a study of the attenuation of ROS production by these ligands. These studies will be carried out in vitro (in test tubes) and in an environment mimicking the biological environment.



Ph.D position



The PhD work will take place at the Laboratory for Coordination Chemistry (LCC), a world-leading coordination and organometallic chemistry research unit in Toulouse, France. The laboratory is equipped with high level facilities and staffed by highly skilled engineers and technicians, providing access to a wide range of techniques. The team benefits from its own financial support as well as dedicated equipment to ensure the successful completion of the project. The "Institut de Chimie de Toulouse" (ICT) also offers the whole community a scientific platform combining high-level characterization techniques equipment (NMR, XRD, Mass, IR, etc.).

The majority of the thesis work will be carried out at the Laboratory for Coordination Chemistry (LCC) in Toulouse, France, in the "Alzheimer, Amyloids and Bio-Inorganic Chemistry" (<https://hureaulab.wixsite.com/equipeflcc>) team directed by Christelle Hureau, Research Director. The work will be supervised by Charlène Esmieu, Research Associate. Weekly meetings will be scheduled with the supervisor to monitor the project progress, in addition to almost daily interaction.

The PhD student's work will be valorized through publications, two of which are necessary for the defense of the thesis. The work will be disseminated to the scientific community through participation in conferences and to the general public through participation in popular science events such as the "Fête de la Science".

The candidate should be motivated, persevering and keen to work at the chemistry/health interface in a multidisciplinary environment. While a background in organic chemistry is preferred, it is not required. Anyway, an interest in bioinorganic chemistry would be an asset.

References

- [1] Christelle Hureau. Role of Metal Ions in Alzheimer's Disease: Mechanistic, Royal Society of Chemistry, pp.170-192, 2022, 978-1-83916-230-5 ;
- [2] *Inorganic Chemistry*, 2019, 58, 20, 13509-13527 ;
- [3] *Chemical Reviews*, 2019, 119, 2, 1221-1322 ;
- [4] *Inorganic Chemistry*. 2024, 63, 5, 2340–2351