Ph.D position available at the Coordination Chemistry Lab in Toulouse

Synthesis and evaluation of new copper ligands for the therapy by chelation in the context of Alzheimer disease

Alzheimer's disease (AD) is the most common neurodegenerative disease and the major cause of dementia throughout the world. This pathology is still incurable since no therapies have so far reach the objective to prevent or even stop its progression. Between 2003 and 2012 more than 200 molecules failed in various stage of clinical trials. In that context, there is a pressing need to develop new therapeutic tools and strategies to help the design of efficient drug candidates.

Although the mechanisms underlying this complex pathology are not yet fully understood, a broad consensus attributes the early development of AD to the amyloid cascade shown in Figure 1A. This process relies on the disturbed equilibrium between the production of a peptide called amyloid-β (Aβ) and its degradation by proteases leading to the extracellular formation of amyloid plaques, a distinctive post-mortem marker of the disease.

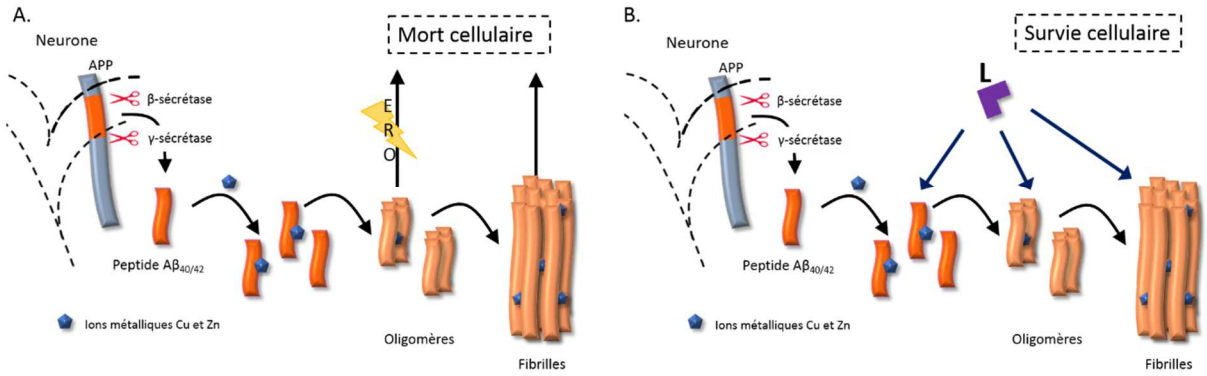

Figure 1 : (A) Schematic representation of the amyloid cascade hypothesis and (B) therapeutic approach by chelation

Moreover, a dysregulation of metal ions, particularly Cu and Zn, is also linked to the amyloid cascade process. Strong evidences have associated the high toxicity of Cu-containing aggregates to their ability to promote the oxidative stress observed in AD *via* the catalytic production of toxic reactive oxygen species (ROS, *Encyclopedia of Inorganic and Bioinorganic Chemistry*, *2018, doi.org/10.1002/9781119951438.eibc2635*). Development of new therapeutic tools and approaches focusing on the molecular mechanisms responsible for the progression of AD is an appealing concept. For the reasons given above, Cu is considered as the therapeutic target. Its removal from Aβ with ligands (L) is a particularly promising approach since it combines the advantages to have an impact on both (i) ROS production and (ii) formation of toxic Aβ aggregates, but it is still in its infancy and requires basic research *(Inorganic Chemistry, 2019, 58, 20, 13509-13527)*.

The present work aim at synthetizing and studying new ligands (L) able to extract copper from Cu-Aβ and to stop the associated ROS production (Figure 1 B.)**.** This project includes the synthesis of the ligand, the characterization (UV-vis, fluorescence, EPR, electrochemistry) of the metallic complexes formed upon metalation of L, the study of the ability of L to extract Cu from Cu-Aβ and the ability of L to prevent ROS formation. The ROS studies will be carried out *in vitro* (in test tubes) and on model cell lines (*in vivo*). Studies depending on the state of aggregation of the peptide will also be undertaken. The improvement of cell survival in the presence of L and Cu-Aβ will be studied. The monitoring of L on a living cell will be done by confocal microscopy resolved in time.

The candidate should be a motivated and perseverant person, willing to work on the interface chemistry / health in a multidisciplinary environment. The candidates should have a background in both organic and inorganic synthesis, as well as in spectroscopic techniques.

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Candidate: The searched candidate has to be an organic+inorganic chemist with strong interest for multidisciplinary research.

The gross salary is 1800 Euros /months and the position is available from the 01.10.2020.

Host Lab and team: Coordination Chemistry Lab in Toulouse (France) and "Alzheimer and amyloid" team (Please consult: https://www.lcc-toulouse.fr for more further) information.

Dead-line for application: 15 June 2020.

To apply : send a CV, a cover letter and your school grades (master) to the following mail addresses AND apply online through the doctoral school website http://www.edsdm.ups-tlse.fr/ in "SDM Ph.D proposals".

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