

Elucidation of some molecular mechanisms at the origin of Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder affecting more than 30 million people worldwide. There is currently no curative medication able to stop the progression of the disease. Only symptomatic treatments with moderate effects are available. One main reason for that is the only partial understanding of the molecular features at the origin of AD. The amyloid cascade hypothesis that would explain the etiology of the disease relies on the complex interactions between the amyloid- β (A β) peptide, metal ions and their biological environment. More explicitly, it has been proposed that the dysregulation of A β production and clearance leading to its accumulation in the synaptic cleft triggers a series of deleterious events, including the formation of A β aggregates.^[1] In addition to the aggregates of A β peptides, metal ions are found over-concentrated in the senile plaques, one post-mortem hallmark of the disease.^[2] They may play a modulating role in the aggregation process, possibly leading to highly toxic species. For redox ions (typically Copper ions), they also have a strong harmful effect via the formation of Reactive Oxygen Species (ROS) that contribute to the oxidative stress detected in AD.^[3] Therefore, studying the interaction of the A β peptide and its aggregates with metal ions is essential for understanding AD.

Aggregation of the A β peptide in the presence of metal ions and ROS formation catalyzed by the Cu(A β) complex have been extensively studied in the last years by the French host group. The step forward is to study the interaction of the A β peptide with membranes as our working hypothesis is that ROS produced in the vicinity of cellular membranes is more toxic than when produced elsewhere.

The study of the three-partners (A β , metal ions, membranes) interactions will benefit from several equipments and methodologies recently implemented by the Japanese host group. It includes the possibility to monitor the A β interaction with model membranes by NMR^[4] and kinetically monitor the key Cu intermediates involved in the reaction of ROS formation by FTIR.^[5]

The project will thus be conducted both in Toulouse and Nara, with at least 12 months in each country, with some support. It aims at investigating at the molecular level the interaction between the A β peptide (in various aggregation states) and metal ions and how these interactions are influenced by the presence of model membranes.

PhD offer: joint project between UPS (University Paul Sabatier – Toulouse) and NAIST (Nara Institute of Science and Technology, Japan). Double doctoral degree.

Host Labs: Coordination Chemistry Lab (UPR 8241, Toulouse, Team: "Alzheimer and amyloids", supervisor: Christelle HUREAU and Laboratory for Supramolecular Science, supervisor: Shun HIROTA)

To apply, please contact: Dr. Christelle HUREAU at Christelle.hureau@lcc-toulouse.fr AND prof. Shun HIROTA at hirota@ms.naist.jp.

Starting Oct. 2018 (in France). Dead-line to apply: 15th of May (the funding is already acquired).

References:

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- [4] H. Kobayashi, S. Nagao and S. Hirota, *Angew. Chem. Int. Ed.* **2016**, *55*, 14019-14022.
- [5] H. Tai, K. Nishikawa, M. Suzuki, Y. Higuchi and S. Hirota, *Angew. Chem. Int. Ed.* **2014**, *53*, 13817-13820.