Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: CEA, BIG, Laboratoire de Chimie et Biologie des Métaux.

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Research project title: **Bcl-xL Amyloidogenesis: role in abnormal apoptosis and neurodegenerative disorders.**

5 Keywords to describe the project: Bcl-xL – Amyloid – Neuroinflammation- Prokineticin - Alzheimer's disease

Description of the project (aims, experimental techniques, recommended background):

Neurodegenerative disorders, i.e. Alzheimer's disease (AD), are associated with the presence of abnormal neuronal apoptosis and the accumulation of various proteins in inclusion bodies. Bcl-xL, a key anti-apoptotic factor may undergo structural changes leading to the formation of amyloid fibers and aggregates in neurons undergoing oxidative stress [1,2]. Such structural changes may confer to Bcl-xL new pro-apoptotic functionalities [3]. The proposed Master2 project aims to characterize (i) the molecular mechanisms of Bcl-xL amyloidogenesis during the inflammatory process, ii) their involvement in the propagation of apoptosis, iii) the effects of two anti-inflammatory molecules, the PKRA505 and PC7 in the control of the amyloid Bcl-xL aggregates-associated neuroinflammation. These molecules are antagonists of the receptors of the prokineticin 2 (PK2) protein. PK2 is a bioactive peptide (also known as Bv8) that promotes neuroinflammation. In vivo, PK2 has been shown to be increased in the ischemic cortex and its antagonisation, using PKR505, or siRNA decreased infarct volume and central inflammation [4]. Hence, we propose to characterize the relationship between amyloid Bcl-xL aggregates and PK2 in the development of neuroinflammatory stress, associated to AD, and to test the potential therapeutic effect of PROKRs antagonists [5]. These experiments will be performed both *in vitro*, using neuron cells, and in AD animal models. We also will determine the status of Bcl-xL in the brain of PK2 knockout model (animal model available in Dr Alfaidy's lab). In conclusion, this project will support the biological significance of Bcl-xL's amyloid aggregate during abnormal neuronal death in relation with PK2. This will provide new insights into the understanding of the development, the prevention and the therapy of neurodegenerative disorders.

Justification that the internship's subject fits with the general theme of GRAL:

The proposed project fits well within the theme of GRAL, as it aims at pursuing our work on the role of Bcl-xl in the development of neuro-inflammatory diseases. We have recently demonstrated that amyloid aggregates forms through apoptosis process. Here we would like to further understand the mechanism by which the aggregates forms, especially those related to the changes in the structural change in the Bcl-xl factor. Also, this project aims at testing potential therapeutic molecule that exhibit anti-neuroinflammatory effects. All molecular tools and knowledge are available for the candidate to conduct a successful Master2 degree.

Relevant publications of the team:

[1] Chenal et al. J Mol Biol. 2012 Jan 20;415(3):584-99; [2] Fakhir F., Landas E., Chenal A., Forge V. and Marquette C. Oxidative metal stress induce amyloïd aggregates formation through apoptosis process. submitted. [3] Fujita et al., 1998, Oncogene 17,1295- 1304. [4] Cheng et al., PNAS, 2012, 109(14):5475-5480. [5] Traboulsi W, et al.Clin Cancer Res. 2017 Nov 15;23(22):7130-7140. Alfaidy et al., Patent PCT/EP2017/08232