Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2018 - 2019

INTERNSHIP PROPOSAL

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

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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 – Apoptosis – Ubiquitination – Neurodegenerative disorders.

Description of the project (aims, experimental techniques, recommended background):
Neurodegenerative disorders, such as Alzheimer's disease and ischemic stroke, 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 a structural change leading to the formation of amyloid fibers and aggregates in neurons undergoing oxidative stress [1,2]. Such structural change may confer to Bcl-xL new pro-apoptotic functionalities [3]. The M2 project proposes to study (i) the molecular mechanisms of Bcl-xL amyloidogenesis during inflammatory apoptosis, and analyze the cell degradation system during the apoptotic response, in animal and cellular models. Particular attention will be paid to whether the ubiquitination state of Bcl-xL is determinant in this amyloid transformation and in particular the role of deubiquitination enzymes, i.e. the specific ubiquitin protease USP8 [4]. For this, the ubiquitination status of Bcl-xL within the amyloid deposits will be defined, in collaboration with Dr. Taillebourg (CEA, BIG, BGE, Gen&Chem team). The M2 project will take advantage of new tools developed recently: conformational antibodies capable of differentiating different aggregates states of Bcl-xL [5] and a specific inhibitor of USP8 [6]. In conclusion, this project will support the biological significance of Bcl-xL's amyloid aggregate during abnormal neuronal death, and will provide new information for the development of prevention and therapy of neurodegenerative disorders.
[1] Chenal et al. J Mol Biol. 2012 Jan 20;415(3):584-99; [2] Fakhir F., Garcia E., Landas E., Chenal A., Forge V. and Marquette C. Oxidative metal stress induce amyloïd aggregates formation through apoptosis process. In preparation. [3] Fujita et al., 1998, Oncogene 17,1295-1304. [4] Jacomin et al., 2015, Plos One 10, e0143078. [5] A. Gonneaud, E. Chartier, S Dartevelle, F. Nato, H. Vitrac, C. Almunia, V. Forge, A. Chenal and C. Marquette. Characterization of conformation-dependent monoclonal antibodies specific to amyloid and non-amyloid Bcl-xL oligomers. In preparation. [6]Patent PCT/EP2017/069919.

Justification that the internship's subject fits with the general theme of GRAL (3 lines):
This project addresses the topics of structural and cellular biology and studies the mechanisms of neuroinflammation involved in the progression of neurodegenerative diseases.

Relevant publications of the team (3 max):

1. Chenal A., Vendrely C., Vitrac H., Karst J.C., Gonneaud A., Blanchet C.E., Pichard S., Salin B., Catty P., Gillet D., Hussy N., Marquette C., Almunia C., Forge V. Amyloid Fibrils Formed by the Programmed Cell Death Regulator Bcl-xL. J Mol Biol. 2012, 415(3):584-99.
2. Pansieri J., Plissonneau M., Heinrich‐Balard L., Morfin J-F, Stransky‐Heilkron N., Rivory P., Mowat P., Dumoulin M., Cohen R., Allémann E., Tóth E., Saraiva MJ., Louis C., Tillement O., Forge V., Lux F. and Marquette C. Gd-nanoparticles functionalization with specific peptides for ß‐amyloid plaques targeting. J Nanobiotechnol, 2016, 14:60.
3. J. Pansieri, M. Plissonneau, N. Stransky-Heilkron, M. Dumoulin, L. Heinrich-Balard, P. Rivory, J-F. Morfin, E. Toth, M.J. Saraiva, E. Allémann, O. Tillement, V. Forge, F. Lux, C. Marquette. Multimodal imaging Gd-nanoparticles functionalised with Pittsburgh compound B or a nanobody for amyloid plaques targeting. Nanomedecine, 2017, 12(14).