Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2017 - 2018

INTERNSHIP PROPOSAL

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Research project title:

Breaking protein complexes controlling membrane architecture and remodelling processes during plasma membrane receptors endocytosis

5 Keywords to describe the project:

Cell signalling, Chemical screening, EGFR, Endocytosis, Ubiquitin system

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

Cell sensing and responding to environmental signals strongly depends on membrane remodelling processes governing the intracellular trafficking of cell surface receptors to or from the plasma membrane. Here, we propose to screen a chemical library of 10,000 compounds *in silico* designed to bind protein interfaces (ANR PPI-Chem, Dr. X. Morelli, Univ. Aix-Marseille) for selecting chemicals breaking the interaction between the oligomeric protein CHMP1B and the ubiquitin protease USP8, which plays a crucial role in membrane abscission at the endosomes. To this end, we will use a fully automated HTRF-based assay in human living cells at the High Throughput Screening platform (HTS-CMBA, Dr. Caroline Barette). Confirmed hits will then be assayed for their ability to prevent the Bimolecular fluorescence complementation of two recombinant proteins USP8-VN and CHMP1B-VN by automated imaging using High Content Screening methods (HCS-CMBA, Dr. Emmanuelle Soleilhac). Finally, the Master student will used the most efficient hit as a powerful chemical probe to dynamically assess the effect of breaking USP8-CHMP1B interaction on epidermal growth factor receptor (EGFR)-dependent signalling in various human cell models relevant for the understanding and targeting of EGFR-dependent oncogenic processes.

Relevant publications of the team:

1. Yang Z, Chen KM, Pandey RR, Homolka D, Reuter M, Janeiro BK, Sachidanandam R, Fauvarque MO, McCarthy AA, Pillai RS. PIWI Slicing and EXD1 Drive Biogenesis of Nuclear piRNAs from Cytosolic Targets of the Mouse piRNA Pathway. **Mol Cell. 2016**;61(1):138-52
2. Martinez A, Soleilhac E, Barette C, Prudent R, Gozzi GJ, Vassal-Stermann E, Pillet C, Di Pietro A, Fauvarque MO, and Lafanechere, L. Novel synthetic pharmacophores inducing a stabilization of cellular microtubules, **Current cancer drug targets 2015**; 15: 2-13.
3. Perrin J, Mortier M, Jacomin AC, Viargues P, Thevenon D, Fauvarque MO. The nonaspanins TM9SF2 and TM9SF4 regulate the plasma membrane localization and signalling activity of the peptidoglycan recognition protein PGRP-LC in Drosophila. **J Innate Immun. 2015**;7(1):37-46.