Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2018 - 2019

INTERNSHIP PROPOSAL

Institute and Group: BIG/ BGE laboratory/ Biomics team & CMBA platform

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Research project title: Development of protease inhibitors as potential anticancer agents/ targeting the enzymatic activity contributing to tumor chemoresistance

5 Keywords to describe the project: protease, DNA damage repair, ubiquitin, sumo, cancer

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

Recently, we have described a novel yeast metalloprotease that degrades aberrant proteins on the chromatin. This unusual enzyme is activated by DNA and genotoxic stress. The human homologue is essential for genomic stability by ensuring replication-coupled DNA repair and completeness of DNA replication. Notably, it is also required for survival of cancer cells treated with common chemotherapeutics such as cisplatin and etoposide. Therefore, the inhibition of this enzyme may be used in combination therapy to increase the potency of well-known anticancer drugs and to overcome tumor chemoresistance.

The goal of M2 project is to develop an enzymatic assay suitable for high-throughput screening (HTS) of protease inhibitors. First, we will produce recombinant protease constructs and set up initial activity assays by determining the optimal experimental conditions such as buffer and salt concentration, pH, cofactor requirements, etc. This will provide assay-relevant information on protease enzymology and allow selecting enzyme and substrate forms as well as detection technology (readout) suitable for the final HTS. Next, the assay will be implemented on the automated High Throughput Screening platform (CMBA) to screen a chemical library of thousands of compounds.

Candidate background: biochemistry/ chemical biology/ pharmacology

Relevant publications of the team (3 max):

1. Balakirev MY*, Mullally JE, Favier A, Assard N, Sulpice E, Rulina A, Lindsey DF, Gidrol X, Wilkinson KD. (2015) Wss1 metalloprotease partners with Cdc48/Doa1 in processing genotoxic SUMO conjugates***. eLife*** Sep 8; 4.
2. Barette C*, Soleilhac E, Charavay C, Cochet C, Fauvarque MO. (2015) Strength and specificity of the CMBA screening platform for bioactive molecules discovery. ***Med Sci*** (Paris). 2015 Apr;31(4):423-31
3. Mugherli L, Burchak ON, Balakireva LA, Thomas A, Chatelain F, Balakirev MY.* (2009) In situ assembly and screening of enzyme inhibitors with surface-tension microarrays. ***Angew Chem Int Ed Engl.*** 2009;48(41):7639-44.

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Justification that the internship's subject fits with the general theme of GRAL (3 lines):

This proposal stems from a collaborative research project, which aims to characterize novel DNA-dependent proteases and study their role in carcinogenesis. We will combine classical biological and biochemical approaches with expert methods developed in partner laboratories in BIG and IBS.


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