Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2017 - 2018

INTERNSHIP PROPOSAL

Institute and Group: BIG, group BGE in collaboration with IBS, group ELMA

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Research project title: Novel metalloproteases in DNA damage repair

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 potentially dangerous proteins on the chromatin. This unusual enzyme is activated by DNA and genotoxic stress. Notably, higher Eukaryotes have proteins homologues to the identified yeast metalloprotease. As the yeast enzyme, human homologue is required for cell survival upon UV irradiation, and is implicated in DNA repair. Both proteins are found on the chromatin and bind molecular chaperon Cdc48. Mutations in human protein result in genomic instability, cellular senescence, progeroid phenotype, and early onset hepato-cellular carcinoma. Importantly, recent data suggest that human protein also works as DNA-dependent metalloprotease.

The goal of M2 project is to characterize biochemically and structurally this putative human metalloprotease. Biochemically, the student will optimize the protocol of the protein expression and purification; will perform enzymatic assays with a panel of substrates and cofactors; and will characterize complexes with partner proteins. Structurally, the student will conduct experiments to identify protein constructs amenable to crystallization; will perform their primary biophysical characterization and initial crystallization trials.

Student background: biochemistry/ molecular biology/ structural biology

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. Colombo M, Girard E, Franzetti B. (2016) Tuned by metals: the TET peptidase activity is controlled by 3 metal binding sites. *Sci Rep.* Feb 8; 6:20876.
3. Appolaire A, Colombo M, Basbous H, Gabel F, Girard E, Franzetti B. (2016) TET peptidases: A family of tetrahedral complexes conserved in prokaryotes. *Biochimie* 122:188-96.