Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group:

Institut de Biologie Structurale.

Group "Extremophiles and Large Molecular Assemblies (ELMA)

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Research project title: Characterization of a novel proteasome targeting machinery

5 Keywords to describe the project: Proteasome regulation, ribosome quality control, large molecular assemblies, X-ray crystallography, Cryo Electron Microscopy, extremophiles.

Description of the project (aims, experimental techniques, recommended background): 10 to 15 lines:

The 26S proteasome is the key component of the ubiquitin-dependent pathway of protein degradation. It controls the levels of the key regulatory proteins in the cell and responsible for protein quality control. The proteasome substrates are selected by several types of regulatory complexes representing important targets in biomedecine, in particular in aging and degenerative diseases. The picture of the proteasome targeting systems is still incomplete. The Master project aims at determining the function and mode of action of a newly identified proteasome regulatory factor, called ZY3. The protein has been recently discovered by the team in extremophilic archaea and is involved in ribosome quality control. Recombinant variants of the ZY3 protein have been produced and the atomic structure of the protein was determined by X-ray crystallography. Its interaction with proteasome subunits and other partners will be studied using a range of biophysical methods such as SPR, AUC, SecMALs. In vitro functional assays will be performed to unravel the effect of ZY3 on substrate targeting and proteasome activities. Native and reconstructed complexes coordinated by the ZY3 regulators will be studied by combining advanced X-ray crystallography, SAXS and Cryo-Electron microscopy. The candidate should have a background in biochemistry and structural biology.

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

The subject is based on integrated structural biology approach aimed at deciphering the dynamics of a complex molecular machine in the cellular context, both in space and time. This project will open the way to major advances in health and environmental biology.

Relevant publications of the team (3 max):

• Colombo, M., Girard, E., and Franzetti, B. (2016) Tuned by metals: the TET peptidase activity is controlled by 3 metal binding sites. ***Scientific reports*** 6, 20876.
• Ibrahim, Z., A. Martel, M. Moulin, H.S. Kim, M. Hartlein, B. Franzetti & F. Gabel, (2017) Time-resolved neutron scattering provides new insight into protein substrate processing by a AAA+ unfoldase. ***Scientific reports* 7**: 40948.
• Cao, S., Engilberge, S., Girard, E., Gabel, F., Franzetti, B & Maupin-Furlow, JA.

(2017) Structural insight into ubiquitin and ubiquitin-like protein recognition and oligomeric states of JAMM/MPN+ proteases. **Structure**. In press