Funded PhD project in Integrated Structural & Cell Biology in Grenoble, France

Title of the PhD project: Arc-RQC - Characterization of the archaeal ribosome quality control system

PhD supervisor: Bruno Franzetti

Host laboratory: Institut de Biologie Structurale - Institut de Biologie Structurale - Extremophiles and Large Molecular Assemblies (ELMA) group

Project summary:
The ribosome quality control system (RQC) is a central player in stress response, ageing and protein misfolding diseases. It modifies defective nascent polypeptides and rout them to the proteasome. The Rqc2 protein represents the core of the RQC machinery. Yet it is not understood how do the Rqc2 interacts with its numerous partners to extend and ubiquitinates polypeptides and extract them toward the proteasome complex. The Arc-RQC project aims to answer these pivotal questions by characterizing the ancestral eukaryotic-like RQC system from hyperthermophilic archaeon. Results will not only improve our knowledge of the RQC molecular mode of action but will also bring evolutionary insights into acquisition of the RQC and ubiquitin-proteasome targeting system in the different kingdoms of life. The structure of the newly identified archaeal Rqc2 protein (arcRqc2) will be determined by combining SAXS and X-ray crystallography. The cellular partners of arc-Rqc2 will be determined using in vitro and in vivo proteomic approaches. The structure of 2 large molecular assemblies already identified as putative Rqc2 partners will be solved using Cryo-Electron Microscopy. Finally, biochemical assays will allow to confirm the functional identity of the novel archaeal RQC components. The project is based on robust preliminary data: SAXS, X-ray Crystallography, Electron Microscopy, first interactomes data sets. The project suits well the topics of the GRAL initiative : dynamics of cellular machines, integrative structural biology of large molecular assemblies. It will involve 3 teams from the GRAL consortium, thus providing to the PhD student an interdisciplinary training.

Preferred skills: Structural Biology; Biochemistry

Student role: The student will be involved in sample production and optimization for cryo-EM, X-ray crystallography and SAXS studies, structures determination and interpretation. In parallel She/He will conduct functional biochemical assays (chaperones and proteases) to demonstrate the role of the newly identified quality control machineries.

Keywords: molecular machine, ribosome quality control, proteasome, archaea

Relevant publications of the team:

1. Mahieu, E., Coves, J., Kruger, G., Martel, A., Moulin, M., Carl, N., Hartlein, M., Carlomagno, T., Franzetti, B., and Gabel, F. (2020) Observing Protein Degradation by the PAN-20S Proteasome by Time-Resolved Neutron Scattering. *Biophys J* **119**, 375-388
2. Carre, L., Girard, E., and Franzetti, B. (2021) Experimental study of proteome halophilicity using nanoDSF: a proof of concept. *Extremophiles* **26**, 1
3. Hogrel, G., Marino-Puertas, L., Laurent, S., Ibrahim, Z., Coves, J., Girard, E., Gabel, F., Fenel, D., Daugeron, M. C., Clouet-d'Orval, B., Basta, T., Flament, D., and Franzetti, B. (2022) Characterization of a small tRNA-binding protein that interacts with the archaeal proteasome complex. *Mol Microbiol* **118**, 16-29
4. Cao, S., Engilberge, S., Girard, E., Gabel, F., Franzetti, B., and Maupin-Furlow, J. A. (2017) Structural Insight into Ubiquitin-Like Protein Recognition and Oligomeric States of JAMM/MPN(+) Proteases. *Structure* **25**, 823-833 e826