Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS/NMR

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Research project title: Integrating protein dynamics into the rational drug design process

5 Keywords to describe the project: NMR, dynamics, HSP90, protein/drug interaction

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

It is generally accepted that protein conformational dynamics, *i.e.* the ability to sample different structures, is central to molecular recognition and ligand binding. Nevertheless, traditional drug discovery neglects the dynamic features and conformational plasticity of proteins. Change in protein dynamics upon ligand binding translates into an entropic contribution to the change in the Gibbs free energy, such information could in principle provide a valuable route for improving the prediction of binding affinities of drug candidates.

The main objective of this project is to provide a better understanding of the interplay between HSP90 protein dynamics and ligand binding. The human Heat Shock Protein 90 (HSP90) is an important target for the treatment of cancer. HSP90 is one of the most abundant proteins in the cytoplasm of human cells, comprising 2–5% of cytosolic proteins under non-stressed conditions. In this project, we will exploit NMR relaxation techniques to investigate the changes in dynamics occurring in HSP90 upon binding to a selected library of resorcinol-based compounds, that have previously shown to possess similar binding affinities (K_D), but differ in the entropic and enthalpic contributions to the binding free energy. The results obtained from our NMR data will allow us to correlate the dynamic changes with the observed differences in the relative importance of entropic and enthalpic binding contributions for the various ligands, and to draw conclusions on the relationship between chemical structure of the ligand and the associated changes in protein dynamics, both locally and remotely, as well as their effect on the binding thermodynamics.

Justification that the internship's subject fits with the general theme of GRAL:

The technologies developed for this project offer new tools to develop and improve rationally new ligands / inhibitors / activators, which will be really interesting for projects of host / pathogen interaction (Axis 1 of the labex GRAL).

Relevant publications of the team :

• Plevin MJ, Bryce DL, Boisbouvier J. *"Direct Detection of CH/π Interactions in Proteins"* **Nature Chemistry** 2, 466-471 (2010).

• Macek P, Kerfah R, Boeri Erba E, Crublet E, Moriscot C, Schoehn G, Amero C, Boisbouvier J "*Unraveling Self-Assembly Pathways of the 468 kDa Proteolytic Machine TET2"* **Science Advances** 3, e1601601 (2017).

• Mas G, Guan J-Y, Crublet E, Colas Debled E, Moriscot C, Gans P, Schoehn G, Macek P, Schanda P, Boisbouvier J **"***Structural Investigation of a Chaperonin in Action Reveals How Nucleotide Binding Regulates the Functional Cycle"* **Science Advances** 4, eaau4196 (2018).