NMR and modelisation study of HSP90 protein dynamics A first step towards the integration of protein dynamics into drug design

Laboratory : Institut Lumiere Matiere
In Cooperation With : Institut de Biologie Structurale (IBS, UMR 5075 : CEA/ CNRS/ Université de Grenoble)
Level : M2
Team(s) : PHYSICOCHEMIE THEORIQUE (A.R. ALLOUCHE)
Contact(s) : LOISON Claire [ claire.loison@univ-lyon1.fr / Tel. 0472431257 ]
Keyword(s) : RMN / Protein / Modeling

Scientific Context :
Proteins are not frozen: their conformations evolve in time, for instance after the interaction with a ligand, or during a catalytic cycle. Conformational dynamics of protein may even become essential to biological phenomena, such as the recognition of physiological partners. Nevertheless, rational Drug Design rarely consider this conformational plasticity.
Nuclear Magnetic Resonance (NMR) and molecular dynamics simulation are complementary techniques which provide information on protein dynamics at various timescales (ns, ps, micro-s). The objective of the project is to bring new tools, based on liquid NMR spectroscopy and simulation in order to understand the contribution of dynamics in the binding of a drug to its biological target. This studies will contribute to improve the success rate of rational Drug Design by incorporating in the protocol a better knowledge of protein conformational dynamics. The N-terminal domain of the Heat-Shock-Protein-90 (NT-HSP90), already well known by the experimental group, is the model of this study. This chaperone is considered as an important therapeutic target: some of its inhibitors can be potential and effective cancer chemotherapeutic drugs and have been examined in clinical trials. Depending on its interaction with various ligand, this protein changes its dynamics (see Fig.(a)). The objective of the internship, and of the following PhD project is to gather knowledge on the protein dynamics using state-of-art NMR relaxation measurements associated to molecular modeling.

Missions :
The experimental step will take place in IBS (Grenoble), in a group internationally recognized for the development of new NMR methodologies to investigate protein complexes. It will consist of the study of NT-HSP90 dynamics. Spin nuclear relaxation measurement will be performed on samples already available in the group. The experimental data, after analysis, will be integrated into the molecular modeling step (in collaboration with the Physico-Chemical Theory Group in ILM, Lyon).

Outlooks :
PhD thesis possible YES. PhD grant available YES. Application deadline : 31th of October 2019