Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: Institut de Biologie Structurale, ELMA Group. Grenoble

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Research project title: Allostery-Origin

5 Keywords to describe the project: Evolutionary biochemistry, ancestral protein resurrection, Structure.

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

Allosteric regulation is the most powerful mechanism to control the catalytic efficiency of enzyme. The objective of the project is to decipher how this property evolved. To achieve this goal, we use a cutting edge methodological approach that links biophysical properties to the history of proteins, namely ancestral protein resurrection. The method provides direct insight into how natural selection has shaped proteins found in nature. By tracing substitutions along a gene phylogeny, ancestral proteins can be reconstructed *in silico* and subsequently synthesized in vitro, purified and then characterized. We have reconstructed the full evolutionary pathway of a large family of enzyme involved in metabolism. Data show that the family is divided in three groups with very different biochemical properties, i.e. allosteric and non-allosteric behaviors. The candidate will purify and determine enzymatic parameters of some of the most relevant ancestral enzymes leading to the various groups. Thanks to this approach it will be possible to see whether or not the ancestral enzymes displayed allosteric behavior. She (he) should have a strong interest in evolution, biochemistry and structural biology. Indeed, we plan to screen various conditions in order to produce proteins crystals suitable for X-rays diffraction studies. Solving the structure of a several billions years old ancestral enzymes would be icing on the cake.

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

The candidate will screen chemical library of the CMBA Grenoble to search efficient inhibitors that targets allosteric sites. Indeed, allosteric binding sites have not faced the same evolutionary pressure as catalytic sites to accommodate an endogenous ligand.

Relevant publications of the team:

Colletier JP, Aleksandrov A, Coquelle N, Mraihi S, Mendoza-Barberá E, Field M, Madern D. Sampling the conformational energy landscape of a hyperthermophilic protein by engineering key substitutions. Mol Biol Evol. (2012); 29:1683-94.

Kalimeri M, Girard E, Madern D, Sterpone F. Interface matters: the stiffness route to stability of a thermophilic tetrameric malate dehydrogenase. Plos One 2014.

Coquelle N, Fioravanti E, Weik M, Vellieux F, Madern D. Activity, stability and structural studies of lactate dehydrogenases adapted to extreme thermal environments. J Mol Biol. (2007); 374 (2):547-62.