UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Internship project Master 2
Year 2018-2019

Laboratory/Institute: Institut de Biologie Structurale **Director:** Prof. Winfried WEISSENHORN
Team: Protein Dynamics and Flexibility (FDP) **Head of the team:** Dr. Martin BLACKLEDGE
Name and status of the scientist in charge of the project: **HDR: yes** X **no** ☐
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Program of the Master's degree in Biology:

☐ Neurosciences and Neurobiology
X Integrative Structural Biology
☐ Immunology, Microbiology, Infectious Diseases
☐ Physiology, Epigenetics, Differentiation, Cancer

Title of the project:

Visualising the assembly of MAPK cell signalling complexes using NMR spectroscopy

Objectives (up to 3 lines):

The project aims at using solution NMR spectroscopy for elucidating the mechanism of action of the intrinsically disordered scaffold protein JIP1 at atomic resolution by studying its interactions with proteins of the mitogen-activated protein kinase (MAPK) cell signaling pathways

Abstract (up to 10 lines):

Mitogen-activated protein kinases (MAPKs) are components of eukaryotic signal transduction networks that enable cells to respond appropriately to extracellular stimuli. Intrinsically disordered proteins (IDPs) ensure signalling specificity in the MAPK pathways by assembling multiple kinases into dynamic signalling complexes. This assembly occurs either through regulatory domains of the kinases themselves, or via an "external" scaffold protein that binds three kinases of a given signalling module. We will rely on nuclear magnetic resonance (NMR) spectroscopy for studying disordered regions of kinases and scaffold proteins and visualise their step-wise assembly into large multi-enzyme complexes that regulate signalling specificity. Elucidating the mechanism of action of these disordered domains is particular pertinent as deregulation of the MAPK pathways has been linked to a number of human cancers. We will provide structural models of IDP complexes controlling specificity thereby paving the way for structure-based development of novel drugs targeting specific steps of these cancer-related pathways.

Methods (up to 3 lines):

Protein expression and purification, characterisation of protein-protein interactions using biophysical techniques, development of solution NMR spectroscopy methods for disordered proteins and their interactions, X-ray crystallography

Up to 3 relevant publications of the team:

(1) Delaforge, Kragelj, Tengo, Palencia, Milles, Bouvignies, Salvi, Blackledge, Jensen. "*Deciphering the dynamic interaction profile of an intrinsically disordered protein using NMR exchange spectroscopy*". **J. Am. Chem. Soc. (2018) 140, 1148-1158**.

(2) Kragelj, Palencia, Nanao, Maurin, Bouvignies, Blackledge Jensen. "*Structure and dynamics of the MKK7-JNK signaling complex*". **Proc. Natl. Acad. Sci. U.S.A. (2015) 112, 3409-3414.**

(3) Kragelj, Ozenne, Blackledge, Jensen. "*Conformational propensities of intrinsically disordered proteins from NMR chemical shifts*". **ChemPhysChem (2013) 14, 3034-3045.**

Requested domains of expertise (up to 5 keywords):

Structural biology, biochemistry, biophysics and NMR