Internship project Master 2
Year 2017-2018

Laboratory: Institut de Biologie Structurale (IBS) **Director:** Prof. Winfried WEISSENHORN
Team: Protein Dynamics and Flexibility by NMR (FDP) **Head of team:** Dr. Martin BLACKLEDGE
Name and status of scientist in charge of the project:
Dr. Malene JENSEN (CR1, CNRS) **HDR yes** X **no** ☐
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Program the Master's degree in Biology:

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

Title of project:

Visualising the assembly of MAPK cell signalling complexes using NMR spectroscopy

Objectives (up to 3 lines):

This project aims at using NMR spectroscopy and other biophysical techniques for elucidating the role of protein intrinsic disorder in the MAPK cell signalling pathways. We will characterize long disordered regions of kinases and scaffold proteins and visualise their assembly into dynamic multi-enzyme complexes.

Abstract (up to 10 lines):

Mitogen-activated protein kinases (MAPKs) are components of eukaryotic signal transduction networks that enable cells to respond to extracellular stimuli. The MAPK pathways display high levels of protein intrinsic disorder, however, current knowledge about signal transmission is essentially limited to crystal structures of folded domains of kinases and phosphatases. Intrinsically disordered proteins (IDPs) play crucial roles in ensuring signalling specificity in the MAPK pathways by assembling multiple kinases into dynamic signalling complexes. Here, we will use NMR spectroscopy for studying disordered regions of kinases and scaffold proteins (up to 500 amino acids in length) and visualize their assembly into large multi-enzyme complexes that regulate MAPK signalling specificity. Deregulation of the MAPK pathways has been strongly linked to a number of human cancers. We will provide structural models of IDP complexes 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) J. Kragelj, A. Palencia, M. Nanao, D. Maurin, G. Bouvignies, M. Blackledge, M.R. Jensen. "*Structure and dynamics of the MKK7-JNK signaling complex*", **Proc. Natl. Acad. Sci. U.S.A. (2015) 112: 3409-3414.**
(2) M.R. Jensen, G. Communie, E. Ribeiro, N. Martinez, A. Desfosses, L. Salmon, L. Mollica, F. Gabel, M. Jamin, S. Longhi, R. Ruigrok, M. Blackledge. "*Intrinsic disorder in measles virus nucleocapsids*", **Proc. Natl. Acad. Sci. U.S.A. (2011) 108: 9839-9844.**
(3) J. Kragelj, V. Ozenne, M. Blackledge, M.R. 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