Master 2 internship project
Year 2019-2020

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:
Dr. Malene JENSEN (DR2, CNRS) **HDR: yes** ☒ **no** ☐
Address: 71 Avenue des Martyrs, 38044 Grenoble
Phone: 0 457 428 668 **e-mail:** malene.ringkjobing-jensen@ibs.fr

Program of the Master's degree in Biology:
☐ Immunology, Microbiology, Infectious Diseases ☒ Integrative Structural Biology
☐ Physiology, Epigenetics, Differentiation, Cancer ☐ Neurosciences and Neurobiology
☐ Planta International

Title of the project:

Revealing the mechanism of action of intrinsically disordered scaffold proteins in MAPK cell signalling by NMR spectroscopy

Objectives (up to 3 lines):

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

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. Intrinsically disordered scaffold proteins play essential roles in mediating signalling specificity by assembling multiple kinases into highly dynamic complexes. Currently, very little is known about how these multi-enzyme complexes are assembled, how the scaffold proteins discriminate between different kinases and how signals are transmitted across the scaffolding complex. We will rely on nuclear magnetic resonance (NMR) spectroscopy for studying scaffold proteins at atomic resolution and visualise their step-wise assembly with kinases of the MAPK pathways. 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, small angle X-ray scattering

Up to 3 relevant publications of the team:

(1) Schneider, Blackledge, Jensen. "*Elucidating binding mechanisms and dynamics of intrinsically disordered protein complexes using NMR spectroscopy*". **Curr. Opin. Struct. Biol. (2018) 54, 10-18.**

(2) 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**.

(3) 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.**

Requested domains of expertise (up to 5 keywords):

Structural biology, biochemistry, biophysics and NMR