UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2020-2021

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:

☐ Immunology, Microbiology, Infectious Diseases X 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 signaling 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 signaling 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 signaling 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 visualize 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 scaffold protein complexes controlling signaling 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, characterization 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) Schneider, Blackledge, Jensen. "*Elucidating binding mechanisms and dynamics of intrinsically disordered protein complexes using NMR spectroscopy*". **Curr. Opin. Struct. Biol. (2019) 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