Master 2 research internship in Integrated Structural & Cell Biology in Grenoble

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Title of the M2 research internship:
New approaches for peptide epitope mapping by NMR spectroscopy

Project summary:
Peptide-protein interactions are at the heart of many cellular processes and the development of selective inhibitors of these complexes represents a promising route for drug discovery. Experimental determination of peptide binding epitopes (i.e. identification of the backbone and side chain atoms of the peptide responsible for the interaction with a protein target) is an essential first step in the design of inhibitors that mimic these epitopes in their bioactive conformation.
Here, we will develop a novel NMR approach for peptide epitope mapping. The idea is to use 1H-13C spectra to observe the peptide in the presence of a small amount of its (high molecular weight) protein target. Chemical exchange saturation transfer (CEST) experiments will be used to monitor the exchange of the peptide between its free and protein-bound states. The CEST experiments will provide the chemical shift difference between free and protein-bound peptide for all carbon atoms of the backbone and side chains thereby allowing to map the peptide binding epitope at unprecedented resolution.
The method will be developed using peptide-protein complexes within the mitogen-activated protein kinase (MAPK) cell signaling pathways. The MAPK proteins (ERK, JNK or p38) recruit their partners by selectively binding to so-called docking site peptides composed of two to three positively charged amino acids and three hydrophobic amino acids. The MAPKs are potential drug targets due to their involvement in human cancers, and the MAPK:peptide interactions represent interesting targets for drug discovery. We will validate our approach on complexes for which the structure of the MAPK:peptide complex has been determined previously by X-ray crystallography and subsequently use the method to map epitopes that are currently unknown due to the lack of crystal structures. Our results will be exploited to identify peptide "hotspots" that can be used in the design of novel inhibitors for cancer therapy.

Keywords:
NMR spectroscopy, mitogen-activated protein kinases, peptide epitope mapping

Relevant publications of the team:
K.K. Rasmussen, A. Palencia, A.K. Varming, H. El-Wali, E. Boeri Erba, M. Blackledge, K. Hammer, T. Herrmann, M. Kilstrup, L. Lo Leggio, M.R. Jensen.

Proc. Natl. Acad. Sci. U.S.A. (2020) 117, 20576-20585. "Revealing the mechanism of repressor inactivation during switching of a temperate bacteriophage"

R. Schneider, M. Blackledge, M.R. Jensen. Curr. Opin. Struct. Biol. (2019) 54, 10-18. "Elucidating binding mechanisms and dynamics of intrinsically disordered protein complexes using NMR spectroscopy"

E. Delaforge, J. Kragelj, L. Tengo, A. Palencia, S. Milles, G. Bouvignies, N. Salvi, M. Blackledge, M.R. Jensen. J. Am. Chem. Soc. (2018) 140, 1148-1158. "Deciphering the dynamic interaction profile of an intrinsically disordered protein by NMR exchange spectroscopy"

J. Kragelj, A. Palencia, M. Nanao, D. Maurin, G. Bouvignies, M. Blackledge, M.R. Jensen. Proc. Natl. Acad. Sci. (2015) 112, 3409-3414. "Structure and dynamics of the MKK7-JNK signalling complex"