GRAL PhD PROJECT 2020-2023

Title of the PhD project: Structure, dynamics and assembly of super-scaffolding complexes in MAPK cell signaling

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Summary of the project: Mitogen-activated protein kinases (MAPKs) are components of eukaryotic signal transduction networks that enable cells to respond to extracellular stimuli. Here, we focus on the JNK signaling pathway whose activation relies on the assembly of a so-called super-scaffolding complex composed of two interacting, intrinsically disordered scaffold proteins, POSH and JIP1, the small GTPase RAC1 and the three sequentially activating kinases DLK, MKK7 and JNK. This super-scaffolding complex ensures specific signal transfer across the entire pathway from the GTPase to JNK through a yet unknown mechanism. We will use nuclear magnetic resonance (NMR) spectroscopy, in combination with X-ray crystallography, biophysics and cellular studies, to obtain an atomic resolution description of how this super-scaffolding complex is assembled, to reveal the interplay between the two scaffold proteins POSH and JIP1 and to elucidate the molecular mechanisms associated with transfer of signals across this highly dynamic complex. The project provides novel insight into the structural, dynamic and mechanistic details underlying the function of scaffold proteins in cell signaling and in general into the regulatory role of intrinsically disordered proteins in biology. In addition, the project provides an important outlook for the development of drugs targeting specific steps of these disease-related signaling pathways.

Keywords: NMR spectroscopy, intrinsically disordered proteins, mitogen-activated protein kinases, scaffold proteins, supramolecular assemblies

Applicant profile: Chemist, biochemist or biophysicist with experience in expression and purification of proteins for structural biology studies. Experience with acquisition and analysis of NMR data and/or biophysical techniques for measuring protein-protein interactions would be an advantage.

Three recent publications of the PhD supervisors

R. Schneider, M. Blackledge, M.R. Jensen. Curr. Opin. Struct. Biol. (2018) 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