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

Supervisor(s):
Malene Jensen, malene.ringkjobing-jensen@ibs.fr
Andrés Palencia, andres.palencia@univ-grenoble-alpes.fr, Institute for Advanced Biosciences, Grenoble

Host laboratory:
IBS, FDP group
https://www.ibs.fr/spip.php?lang=en

Title of the M2 research internship:
Exploring the inhibition of a new drug target of the human parasite Cryptosporidium by NMR spectroscopy

Project summary:
Apicomplexan parasites represent a public health concern because of the scarcity of effective therapeutic treatments and due to the emergence of resistance in some regions of the world. Cryptosporidium is an apicomplexan parasite that causes cryptosporidiosis, a severe gastrointestinal disease fatal for young children and life-threatening for immunocompromised adults. To date, there is no vaccine and the current treatment for cryptosporidiosis is not optimal as it shows poor efficacy and high toxicity. The development of new drugs against cryptosporidiosis is therefore needed.
The Cleavage and Polyadenylation Specificity Factor (CPSF) complex consists of several protein subunits that together are responsible for the maturation of newly transcribed RNAs in the nucleus. The structural organization of the complex is controlled by the intrinsically disordered scaffold protein FIP1, placed at the core of the complex, where it binds to multiple CPSF subunits, including the poly-adenosine polymerase (PAP) responsible for the addition of the poly-adenosine tail to the cleaved mRNA. The CPSF complex represents a promising drug target for example via inhibiting the catalytic site of PAP or via blocking the recruitment of PAP to the FIP1 scaffold.
The goal of the project is to test the binding of a library of 400 chemically diverse compounds that were selected by in silico molecular docking to PAP starting from a collection of 1.2 million compounds. NMR will be used to screen this library using a combination of saturation transfer difference (STD), relaxation dispersion and chemical exchange saturation transfer (CEST) techniques. Hits will be characterized in terms of affinity and thermodynamics by isothermal titration calorimetry (ITC), subjected to X-ray crystallography studies and the best compounds will be tested in vivo.
The project will be carried out in collaboration with researchers at the IAB Grenoble (Palencia's group) and is supported by connections to medicinal chemistry in pharmaceutical industry.

Keywords:
drug discovery, NMR spectroscopy, apicomplexan parasites

Relevant publications of the team:
L. Mariño Pérez, F. S. Ielasi, L. M. Bessa, D. Maurin, J. Kragelj, M. Blackledge, N. Salvi, G. Bouvignies, A. Palencia, M.R. Jensen "Visualizing protein breathing motions associated with aromatic ring flipping" Nature (2022) In press

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

C. Swale, A. Bougdour, A. Gnahoui-David, J. Tottey, S. Georgeault, F. Laurent, A. Palencia, M.-A. Hakimi "Metal-captured inhibition of pre-mRNA processing activity by CPSF3 controls Cryptosporidium infection". Sci. Trans. Med. (2019) 11, eaax7161

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

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