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

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

Title of the M2 research internship:
Investigating the role of intrinsic disorder in the replication machinery of SARS-CoV-2 using NMR spectroscopy and integrated structural biology

Project summary:
The processes of replication and transcription of viral RNA represent important targets for viral inhibition, and the development of rational strategies to achieve this end requires a molecular understanding of the viral replication cycle. The nucleoprotein of SARS-CoV-2 is the most abundant protein expressed by the virus and comprises a number of important mutations associated with known variants of concern. This natural target for the development of antiviral inhibitors comprises long intrinsically disordered domains which confer a high degree of flexibility – essential for its biochemical activity – but which also render it particularly challenging to characterize using classical structural biology.
The Protein Dynamics and Flexibility by NMR group at the IBS recently described the structure and dynamics of N for the first time at atomic resolution, revealing the extensive conformational changes associated with interaction with its essential viral cofactor nsp3. The student will follow up on this study, investigating RNA-binding of N during nucleocapsid formation, describing the molecular basis of regulation of the function of N when hyper-phosphorylated, and describing the functional impact of important mutations of N associated with known variants of concern. This work will hopefully identify novel directions for the development of viral inhibitors.

Keywords:
NMR spectroscopy, SARS-CoV-2, electron microscopy

Relevant publications of the team:

The intrinsically disordered SARS-CoV-2 nucleoprotein in dynamic complex with its viral partner nsp3a. Bessa LM, Guseva S, Camacho-Zarco AR, Salvi N, Mariño Perez L, Maurin D, Botova M, Malki A, Nanao M, Jensen MR, Ruigrok R, Blackledge M* Science Advances (2022).

Molecular basis of host-adaptation interactions between influenza virus polymerase PB2 subunit and ANP32A Camacho-Zarco AR, Kalayil S, Maurin D, Salvi N, Delaforge E, Milles S, Jensen MR, Hart DJ, Cusack S, Blackledge M* Nature communications 11, 1-12 (2020)

Measles virus nucleo-and phosphoproteins form liquid-like phase-separated compartments that promote nucleocapsid assembly. Guseva, Milles, Jensen, Salvi, Kleman, Maurin, Ruigrok, Blackledge M* Science Advances eaaz7095 (2020)

Adamski, Salvi, Magnat, Milles, Jensen, Abyzov, Moreau, Blackledge*. A unified description of intrinsically disordered protein dynamics under physiological conditions using NMR spectroscopy. J Am Chem Soc, 141, 17817-17829 (2019)

Milles S, Jensen MR, Lazert C, Guseva S, Ivashchenko S, Communie G, Maurin D, Gerlier D, Ruigrok R,* Blackledge M*. An ultraweak interaction in the intrinsically disordered replication machinery is essential for measles virus function. Science Advances, 4, eaat7778 (2018)

Salvi, Abyzov, Blackledge. Analytical Description of NMR Relaxation Highlights Correlated Dynamics in Intrinsically Disordered Proteins. Angew Chem Int Ed Engl. 5614020-14024 (2017)

Abyzov, A., Salvi, N., Schneider, R., Maurin, D., Ruigrok R, Jensen MR, Blackledge M*. Identification of Dynamic Modes in an Intrinsically Disordered Protein using Temperature Dependent NMR Relaxation. J Am Chem Soc, 138, 6240–6251 (2016)