Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: Blackledge Group (Protein Dynamics and Flexibility by NMR) Institut de Biologie Structurale

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Research project title: Ultra-weak interaction between the intrinsically disordered phosphoprotein and the nucleoprotein of Measles. An exciting target for Measles inhibition.

5 Keywords to describe the project: Intrinsically disordered proteins, protein dynamics, nuclear magnetic resonance spectroscopy, protein-protein interactions, molecular complexes

Description of the project (aims, experimental techniques, recommended background): 10 to 15 lines:

Intrinsically disordered proteins play crucial roles in biology although their interaction mechanisms remain very poorly understood. Measles virus genome encapsidation is essential for viral replication, and is controlled by the intrinsically disordered phosphoprotein (P) which interacts with the nucleoprotein (N) prior to nucleocapsid assembly. Intriguingly, all paramyxoviruses harbour highly disordered N-terminal domains (P_{NTD}), that are hundreds of amino acids in length, and whose function remains unknown. Using nuclear magnetic resonance (NMR) spectroscopy we recently described the structure and dynamics of the 90 kDa N^0P_{NTD} complex, comprising 450 disordered amino acids. NMR revealed the existence of an ultra-weak N-interaction motif, hidden within the highly disordered P_{NTD}. Mutation of this linear motif abolishes viral transcription/replication in cell-based mini-genome assays comprising integral viral replication machinery. The essential mechanism appears to be conserved across Paramyxoviridae, opening unique new perspectives for drug development against this family of pathogens. The candidate will use NMR, combined with complementary biophysical approaches such as fluorescence and small angle scattering, combined with simulation, to understand the molecular basis of this inhibitory behavior, and in particular to identify inhibitory strategies that target the newly discovered binding site. An interest in biophysics or biophysical chemistry is appropriate.

Justification that the internship's subject fits with the general theme of GRAL (3 lines):

The project aims to use NMR and, in combination with fluorescence and small angle scattering, to develop inhibitory strategies that can be used to target the newly discovered interaction site on the disordered domain of the P protein that is essential for replication of Measles virus.

Relevant publications of the team (3 max):

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

Self-Assembly of Measles Virus Nucleocapsid-like Particles: Kinetics and RNA Sequence Dependence. Milles S, Jensen M, Communie G, Maurin D, Schoehn G, Ruigrok R, Blackledge M *Angew Chemie Intl Edition*, 128, 9502–9506 (2016)

Visualizing the molecular recognition trajectory of an intrinsically disordered protein using multinuclear relaxation dispersion NMR. Schneider R, Maurin D, Communie G, Kragelj J, Hansen F, Ruigrok R, Jensen M, Blackledge M *J Am Chem Soc* 137, 1220 (2015)