UFR CHIMIE & BIOLOGIE Université Grenoble Alpes

Master in Chemistry

Sujet de stage de Master 2 (1 page max.)

Laboratoire : Institut de Biologie Structurale CEA-CNRS-UGA
Directeur : Winfried Weissenhorn

Intitulé de l'équipe : Protein dynamics and flexibility by NMR Responsable : Martin Blackledge
Nom et Qualité du Responsable du Stage : HDR : oui
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Parcours de Master 2: Chemistry for Life Sciences (CLS)

Titre du sujet :
NMR characterisation of a highly dynamic, multivalent protein-protein interaction essential for adaptation of avian influenza to humans

Objectifs visés du stage (5 lignes max) :
Use of advanced NMR methodology to measure NMR parameters allowing the spatial and temporal nature of the interaction between an intrinsically disordered host protein and its viral partners to be described at atomic detail. Analysis of experimental data in combination with advance molecular modelling. Comparison of the dependence of the interaction on known adaptive mutations.

Intérêts pédagogiques et compétences visées (5 lignes max) :
The use of state-of-the-art high-resolution NMR spectroscopy to describe the behaviour of intrinsically disordered proteins at the atomic level provides a unique insight into this vast family of proteins, whose behaviour lies beyond the reach of standard structural biology, and machine-learning based prediction, due to their highly dynamic nature. Nevertheless, intrinsically disordered proteins represent more than one third of all known proteomes, and therefore lie at the very frontier of contemporary structural biology.

Résumé :

The interest of our group focuses on the study of protein dynamics using NMR spectroscopy associated with complementary experimental biophysics and molecular simulation. Proteins are inherently dynamic on a vast range of time and length scales, exhibiting conformational fluctuations that are essential for function. Intrinsically disordered proteins (IDPs) or regions (IDRs) represent extreme examples where flexibility defines molecular function. We are interested both in the nature of these motions, developing technology to describe the underlying physics, and their application to important biological problems such as the role of disorder in the replication of important human viruses. A significant part of our activity is dedicated to the use of advanced NMR methodology to describe the molecular mechanisms controlling the interactions of IDPs with their partners.[1]

Influenza A viruses (IAVs) are responsible for 3-5 million cases of acute disease every year, resulting in 250-500 thousand deaths. IAV subtypes, notably H5N1 that is currently ravaging bird and diverse mammal populations globally, represent major pandemic threats. Replication in human cells requires adaptive mutation in a very dynamic region (627-NLS) of the viral polymerase (Pol), compensating differences between intrinsically disordered domains of an essential host protein that is hijacked by the virus to infect the host cell. We recently demonstrated the multivalent nature of this interaction, and that the affinity is greatly enhanced due to human-adaptative mutation.[2]

Novel structural and dynamic parameters will be measured by the successful candidate, providing sufficient resolution to distinguish the physico-chemical characteristics of this multivalent interaction. Advanced molecular modelling will be used to interpret the experimental data to further understand the molecular basis of host adaptation of this extremely virulent pathogenic factor.

1. Bessa et al *Science Advances* (2022), Guseva, Schnapka et al *JACS* (2023)
2. Camacho-Zarco et al *Nature Communications* (2020), Camacho-Zarco, Yu et al *JACS* (2023)

Approches & matériels utilisés (5 lignes max) :
State-of-theart high-resolution solution state NMR spectroscopy. Paramagnetic NMR. Preparation of isotopically labelled protein samples for observation of data at atomic resolution. Advanced molecular modelling of intrinsically disordered proteins on the basis of NMR data – ensemble analysis. NMR relaxation dispersion and relaxation to describe the timescales of molecular motions, and the kinetics of molecular interaction.

Domaines de compétences souhaitées du candidat (3 lignes max):
Chemistry, biochemistry, biophysics or physics.

Dates du stage : January to June 2026