

## Postdoctoral position using NMR and integrated structural biology to describe the role of intrinsic disorder in viral replication (Influenza, Measles, SARS-CoV-2)

Blackledge Lab (Protein Dynamics and Flexibility by NMR)

Institute of Structural Biology, Grenoble, France.

**Project description:** Despite major advances made over the last decade both in cryo-electron microscopy and in protein structure prediction, a significant fraction of all proteomes remains beyond the reach of structural biology due to their highly dynamic or disordered nature. NMR spectroscopy is the only tool capable of describing such systems at atomic resolution.

The molecular mechanisms regulating the functional modes of intrinsically disordered proteins (IDPs) remain poorly understood. In our group we use state of the art NMR spectroscopy to describe the conformational dynamics of highly disordered assemblies as a function of their environment (dilute, crowded, phase separated or *in cellulo*) and to map their molecular interaction trajectories in time and space.

The successful candidate will join a multi-disciplinary team investigating the physical role of highly dynamic proteins involved in viral replication, in particular SARS-CoV-2, influenza virus and measles, and to exploit this information to develop novel inhibitors, to crack the still unsolved challenge of ‘*Drugging the Undruggable*’.

**Profile(s):** We are seeking highly motivated post-doctoral researchers to study the functional modes of highly dynamic assemblies involved in the replication of pathogenic RNA viruses (SARS-CoV-2, Measles, Influenza).

The project lies at the interface of biology, chemistry and physics and will mainly exploit state-of-the-art NMR spectroscopy, together with MD simulation (atomic/coarse grained), fluorescence spectroscopy and imaging, X-ray crystallography, cryo-EM and SAXS. We are looking for candidates who are interested in applying physico-chemical approaches to resolve fascinating biological problems. Candidates should have a PhD in biophysics or biomolecular NMR-related subject. Interested candidates should send a cv, motivation letter and the names of two referees to [martin.blackledge@ibs.fr](mailto:martin.blackledge@ibs.fr) or write to [martin.blackledge@ibs.fr](mailto:martin.blackledge@ibs.fr) for more details.

**Grenoble:** Capital of the French Alps, Grenoble is a world-renowned scientific hub with a strong international flavour. It is a pleasant city, situated at the foot of three mountain ranges offering many possibilities for cultural, outdoor and sporting activities. Grenoble is served by international and national airports and a high-speed rail network, lies three hours from Paris and the French riviera, and is close to Italy and Switzerland <https://www.ibs.fr/en/careers/about-grenoble/?lang=en>

**Facilities:** The IBS is situated on the European Photon and Neutron campus together with its European partners, the European Molecular Biology Laboratory (EMBL), the European Synchrotron Radiation Facility, and the Institute Laue-Langevin. This unique site provides access to state of the art equipment to analyze biological systems at different time and length scales. The EPN site represents a true hub of integrated structural and dynamic biology.

The IBS itself provides a lively international working environment with state-of-the-art NMR facilities (950, 850, 700 and 600MHz NMR spectrometers with both liquid-state cryoprobes and state-of-the-art solid-state technology), dedicated wet-lab facilities for cloning, expression and purification of proteins and state-of-the-art imaging facilities.

### Blackledge research group:

<http://www.ibs.fr/groups/protein-dynamics-and-flexibility/?lang=en>

<https://scholar.google.com/citations?user=m7f8QWQAAAAJ&hl=en>

### Recent publications giving examples of the type of work we do in this field

A specific phosphorylation-dependent conformational switch in SARS-CoV-2 nucleocapsid protein inhibits RNA binding. Botova, Camacho-Zarco, Tognetti, Bessa, Guseva, Mikkola, Salvi, Maurin, Herrmann, Blackledge *Science Advances* 10, eaax2323 (2024)

Multivalent dynamic colocalization of avian influenza polymerase and nucleoprotein by intrinsically disordered ANP32A reveals the molecular basis of human adaptation. Camacho-Zarco, Yu, Krischuns, Dedeoglu, Maurin, Bouvignies, Crepin, Ruigrok, Cusack, Naffakh, Blackledge *J Am Chem Soc*, 145, 20985 (2023)

Liquid-liquid phase separation modifies the dynamic properties of intrinsically disordered proteins Guseva, Schnapka, Adamski, Maurin, Ruigrok, Salvi, Blackledge *J Am Chem Soc* 145 10548 (2023)

NMR Provides Unique Insight into the Functional Dynamics and Interactions of Intrinsically Disordered Proteins Camacho-Zarco, Schnapka, Guseva, Abyzov, Adamski, Milles, Jensen, Zidek, Salvi, Blackledge *Chemical Reviews* 122, 9331 (2022)

The intrinsically disordered SARS-CoV-2 nucleoprotein in dynamic complex with its viral partner nsp3a. Bessa, Guseva, Camacho-Zarco, Salvi, Mariño Perez, Maurin, Botova, Malki, Nanao, Jensen, Ruigrok, Blackledge *M Science Advances* 8, eabm4034 (2022).

Molecular basis of host-adaptation interactions between influenza virus polymerase PB2 subunit and ANP32A Camacho-Zarco, Kalayil, Maurin, Salvi, Delaforge, Milles, Jensen, Hart, Cusack, Blackledge *Nature Communications* 11, 1, (2020)

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

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

Solvent-dependent segmental dynamics in intrinsically disordered proteins. Salvi, Abyzov, Blackledge *Science Advances* 5, eaax2348 (2019)

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