Funded PhD project in Integrated Structural & Cell Biology in Grenoble, France (2025-2028)

Title of the PhD project:
Unravel structure-function relationships of the Respiratory Syncytial Virus RNPs

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Host laboratory (UMR): Institut de Biologie Structurale (IBS)

Host laboratory website: https://www.ibs.fr/

Host team/group: Microscopic Imaging of Complex Assemblies (MICA)

Team website, if any: https://www.ibs.fr/en/research/assembly-dynamics-and-reactivity/microscopic-imaging-of-complex-assemblies-mica-group-i-gutsche/?lang=en

Project summary:
Respiratory syncytial virus (RSV) is the leading cause of child bronchiolitis and pneumonia, with a burden on the elderly comparable to that of influenza. Although prophylactic options, such as vaccines and monoclonal antibodies, have recently become available, no effective therapeutic treatment yet exists for patients in need. Intracellular transcription and replication of RSV genetic material are critical steps for spreading infection, making them attractive therapeutic targets; however, the molecular mechanisms involved remain poorly understood at the structural level. These functions are carried out by the viral ribonucleoprotein particles (RNPs), composed of the viral genomic RNA enwrapped into a helical nucleocapsid by a dedicated nucleoprotein, the viral RNA polymerase with its phosphoprotein cofactor, and a transcription factor. While structures of the individual RNP components are mostly known, RNPs reconstituted from these components are non-functional. We have recently designed a way to assemble active miniature RNPs. Leveraging this exciting advancement, this PhD project will be focused on producing functional miniature RNPs locked in the transcription initiation state and determining their 3D structures by high resolution 3D cryo-electron microscopy (cryo-EM). The structural insights gained will be integrated with functional and dynamic information from our teams and partners to create the first molecular mechanistic model of RSV RNA synthesis.

Student role:
This work will enable the PhD student to gain a solid expertise in complementary structural virology techniques, ranging from mammalian cell culture, transfection, and miniature RNP and NC purification, to their functional and structural characterisation, with a particular focus on 3D cryo-EM and image analysis. The student will be included in a network of young MICA and VIM researchers focused on various aspects of the RSV genome synthesis and virion assembly, and have numerous mutually beneficial collaboration opportunities.

Keywords:
Cryo-electron microscopy, cryo-EM, high resolution 3D image analysis, structural biology, virology, Respiratory Syncytial Virus, RSV

Relevant publications of the team:
1). Structural landscape of the respiratory syncytial virus nucleocapsids. Gonnin L, Desfosses A, Bacia-Verloop M, Chevret D, Galloux M, Éléouët JF, Gutsche I. Nature Communications 2023 Sep 15;14(1):5732. doi: 10.1038/s41467-023-41439-8. PMID: 37714861
2). Orally efficacious lead of the AVG inhibitor series targeting a dynamic interface in the respiratory syncytial virus polymerase. Sourimant J, Lieber CM, Yoon JJ, Toots M, Govindarajan M, Udumula V, Sakamoto K, Natchus MG, Patti J, Vernachio J, Plemper RK. Science Advances 2022 Jun 24;8(25):eabo2236. doi: 10.1126/sciadv.abo2236. PMID: 35749502
3). 4'-Fluorouridine is an oral antiviral that blocks respiratory syncytial virus and SARS-CoV-2 replication. Sourimant J, Lieber CM, Aggarwal M, Cox RM, Wolf JD, Yoon JJ, Toots M, Ye C, Sticher Z, Kolykhalov AA, Martinez-Sobrido L, Bluemling GR, Natchus MG, Painter GR, Plemper RK. Science 2022 Jan 14;375(6577):161-167. doi: 10.1126/science.abj5508. PMID: 34855509

Skills/Qualifications:
Structural biology (interest in learning cryo-EM and advanced 3D cryo-EM image analysis is essential), computing (calculations will be run on a high-performance computing cluster, day-to-day computing will be done in linux environment, knowledge of python or desire to learn it would be an asset); skills in biochemistry (mammalian cell culture, protein purification) would be an advantage.