Strikingly different roles of SARS-CoV-2 fusion peptides uncovered by neutron scattering

A. Santamaria[1,2], A. Maestro[1,3,4], N. Zaccai[5], E. Guzmán[2], G. Fragneto[1,6]

[1]*Institut Laue-Langevin, Grenoble, France*

[2]*Universidad Complutense de Madrid, Spain*

[3]*Centro de Física de Materiales (CSIC, UPV/EHU) San Sebastián, Spain*

[4]*IKERBASQUE—Basque Foundation for Science, Plaza Euskadi 5, Bilbao, 48009 Spain*

[5]*Cambridge Institute for Medical Research, University of Cambridge, UK*

[6]*École doctorale de Physique, Université Grenoble Alpes, 38400 Saint-Martin-d'Héres, France*

santamariaa@ill.fr

SARS-CoV-2 is an encapsulated virus responsible for a lethal respiratory illness since its outbreak at the end of 2019. It consists of a lipid envelope and a set of structural membrane proteins that include the envelope, membrane and *spike* (S) proteins, which are responsible for virion assembly. Interestingly, the *fusion domain of the spike protein* triggers the fusion between viral and host membranes, initializing the infection. However, the molecular mechanism regulating this process is not deeply understood. Our approach [1] has been to study the interaction of several putative *fusion peptides (FPs)* at or near the N-terminus of S2 subunit with model membranes in the form of monolayers, bilayers and small unilamellar vesicles, composed of both synthetic lipids and natural lipids extracted from yeast cells. The multi-technique approach exploited in this work implied the use of spectroscopic, interfacial and scattering techniques, particularly neutron reflectometry (NR). NR revealed that FPs assume different functions in the initiation of viral infection. The results obtained here especially shed light on the critical role of FP1 (the N-terminus of the Spike fusion domain), which is able to fully penetrate membranes, in a Calcium-dependent manner (**Figure 1**), and FP4, whose high binding affinity (**Figure 2**) enables it to work as a bridge between membranes. Moreover, this work also provides a powerful interdisciplinary framework for future investigations of eukaryotic and viral membranes fusion mechanism.

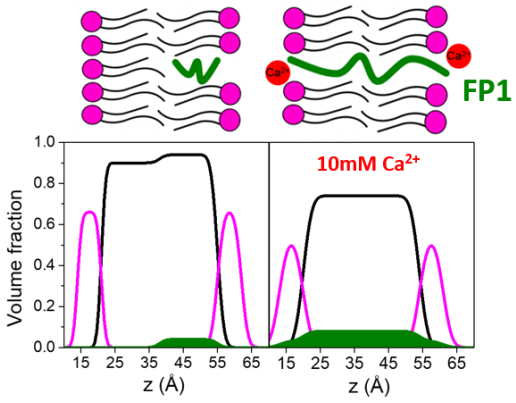

Figure 1. Sketches and volume fraction profiles, from NR, showing FP1 inserted in the membrane.

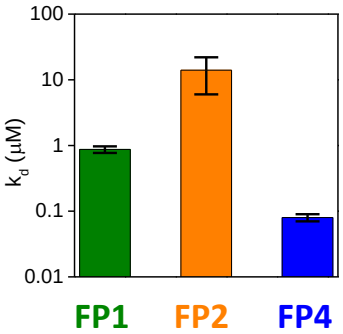

Figure 2. Values of dissociation constant of FPs to an *in vitro* plasma membrane-mimicking system.

1. A. Santamaria, K. C. Batchu, O. Matsarskaia, S. F. Prévost, D. Russo, F. Natali, T. Seydel, I. Hoffmann, V. Laux, M. Haertlein, T. A. Darwish, R. A. R., G. Corucci, G. Fragneto, A. Maestro, and N. R. Zaccai, *J. Am. Chem. Soc.* 2022, **144** (7), 2968-2979. DOI: 10.1021/jacs.1c09856.