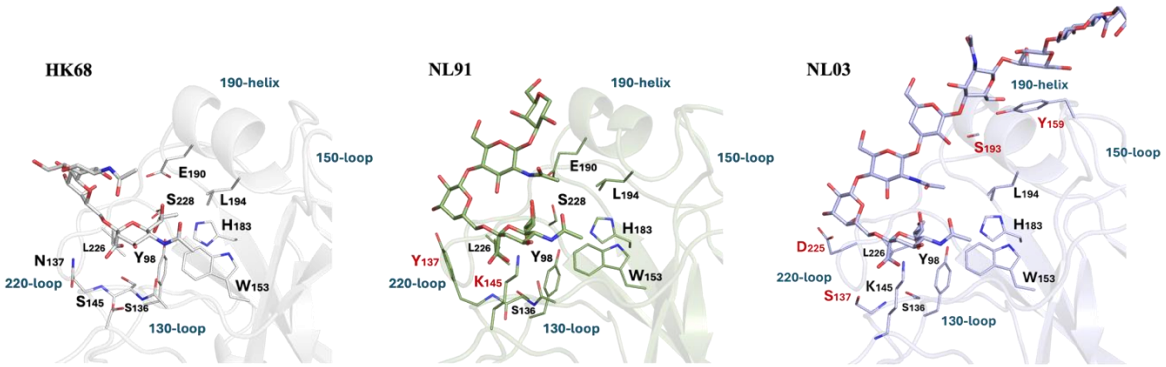
PROBING ALTERED RECEPTOR SPECIFICITIES OF ANTIGENICALLY DRIFTING HUMAN H3N2 VIRUSES BY CHEMOENZYMATIC SYNTHESIS, NMR, AND MODELING

Luca Unione

CICbioGUNE, Basque Research & Technology Alliance (BRTA), Bizkaia Technology Park, Building 800, 48160 Derio, Bizkaia, Spain
Ikerbasque, Basque Foundation for Science, Euskadi Plaza 5, 48009 Bilbao, Bizkaia, Spain
lunione@cicbiogune.es

Human H3N2 influenza A viruses (IAVs) have continuously evolved evading neutralization by antibodies elicited by prior infections or vaccination. Through this process, known as antigenic drift, the viral hemagglutinin (HA) protein undergoes substantial sequence divergence while preserving structure and function. Most of the accumulated mutations take place in the most exposed parts of the globular head of HA, where binding occurs with sialic acid-containing receptors of host cells. Receptor binding modes of IAVs usually co-evolve by orchestrated mutations of several amino acids that allow immune evasion but maintain glycan binding capabilities. As a result, A/H3N2 viruses which are the leading cause of severe seasonal influenza illness resulted in altered receptor binding properties. Predicting influenza evolution requires an understanding, at a molecular level, of how mutational changes shape glycan recognition. However, comprehensive analysis of such epistatic networks across HA proteins remains challenging. Our work contributes to examine the binding modes of such drifted hemagglutinins. We employ a multidisciplinary approach which combines chemical synthesis, protein expression, and high-resolution binding studies to detail viral proteins/receptors interactions. The results contribute to understand viral proteins evolution which is important for vaccine design and for the development of predictive models of IAV variants.



Acknowledgements
This research has received funding from the European Research Council (ERC) under the European Union's ERC Starting Grant 2023 under grant agreement No. 101117639. -Glyco13Cell).

References:
1. Unione L, Ammerlaan ANA, Bosman GP, Uslu E, Liang R, Broszeit F, van der Woude R, Liu Y, Ma S, Liu L, Gómez-Redondo M, Bermejo IA, Valverde P, Diercks T, Ardá A, de Vries RP, Boons GJ. *Nat Commun*. **2024**, 15, 2979.
2. Broszeit F, van Beek RJ, Unione L, Bestebroer TM, Chapla D, Yang JY, Moremen KW, Herfst S, Fouchier RAM, de Vries RP, Boons GJ. *Nat Commun*. **2021**, 12, 5449.