Contribution ID: **41** Type: **Oral contribution**

Generative model of SARS-CoV-2 variants under immune pressure unveils viral escape potential

Tuesday 8 July 2025 14:30 (50 minutes)

The evolutionary trajectory of SARS-CoV-2 is governed by competing pressures for ACE2 binding, structural viability and escape from neutralizing antibodies targeting its receptor-binding domain (RBD). Here, we present a modular framework that quantifies immune selection and predicts antibody resilience beyond single mutations or known variants, by integrating deep mutational scanning (DMS) measurements of ACE2 affinity and escape profiles for 31 monoclonals with a generative sequence model trained on pre-pandemic Coronaviridae. To assess the escape potential of individual antibodies, we designed RBD variants under pressure from four clinically relevant antibodies (SA55, S2E12, S309, VIR-7229). Of 22 tested designs, bearing up to 21 mutations from Wuhan, 50% expressed as stable protein. Binding assays confirm that S309 and VIR-7229 retain recognition across diverse mutation combinations. DMS-informed mutational effects confered strong predictive power, successfully forecasting which antibodies can be subverted by our designed backgrounds. Finally, by identifying negatively correlated escape routes, we prioritize antibody combinations with minimal shared vulnerabilities. By quantitatively linking viral adaptation to antibody resistance profiles, this model provides a predictive foundation for optimizing therapeutic strategies and enhancing long-term pandemic preparedness.

Author: MONASSON, Remi

Presenter: MONASSON, Remi