



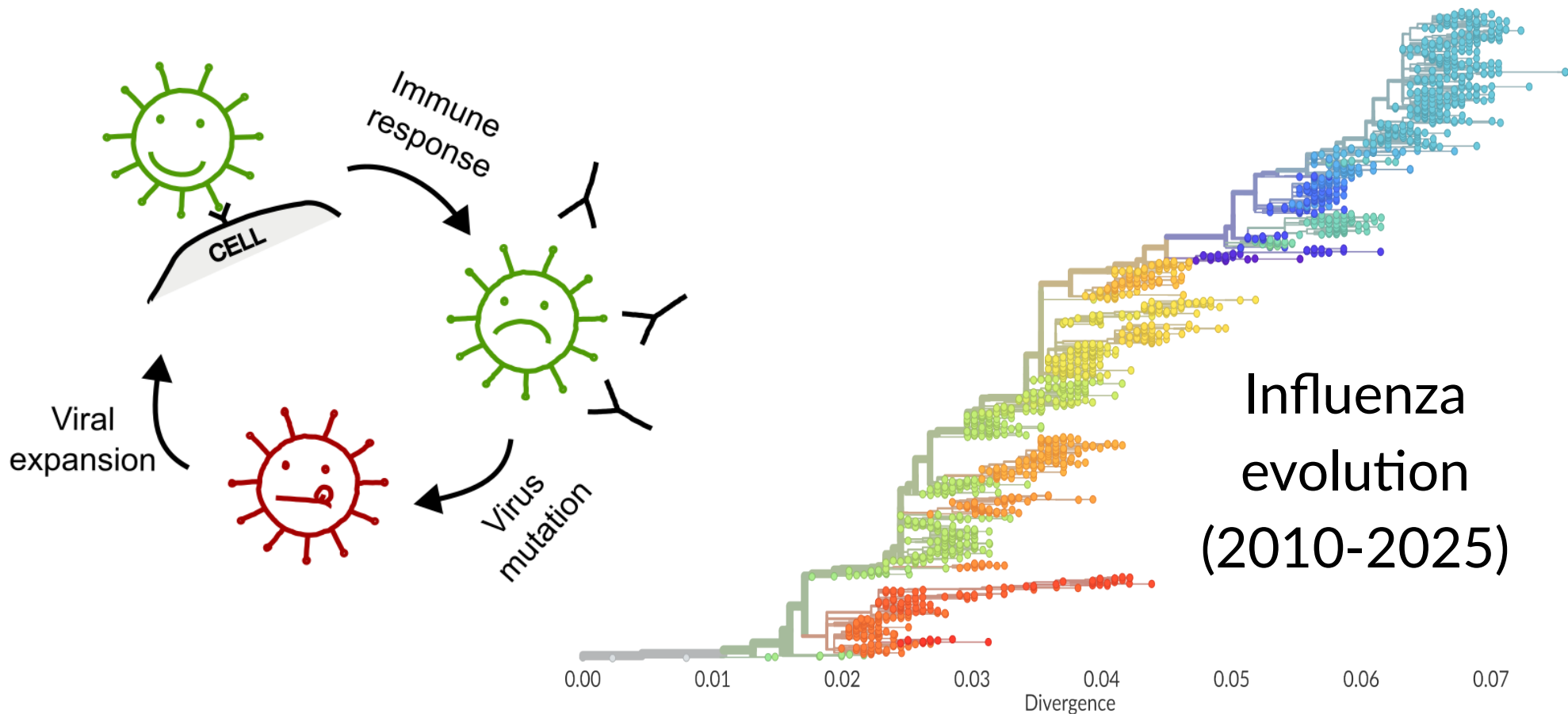
Protein Paleontology

Thomas Dupic

September 17th, 2025 – Centuri Days



Viral evolution

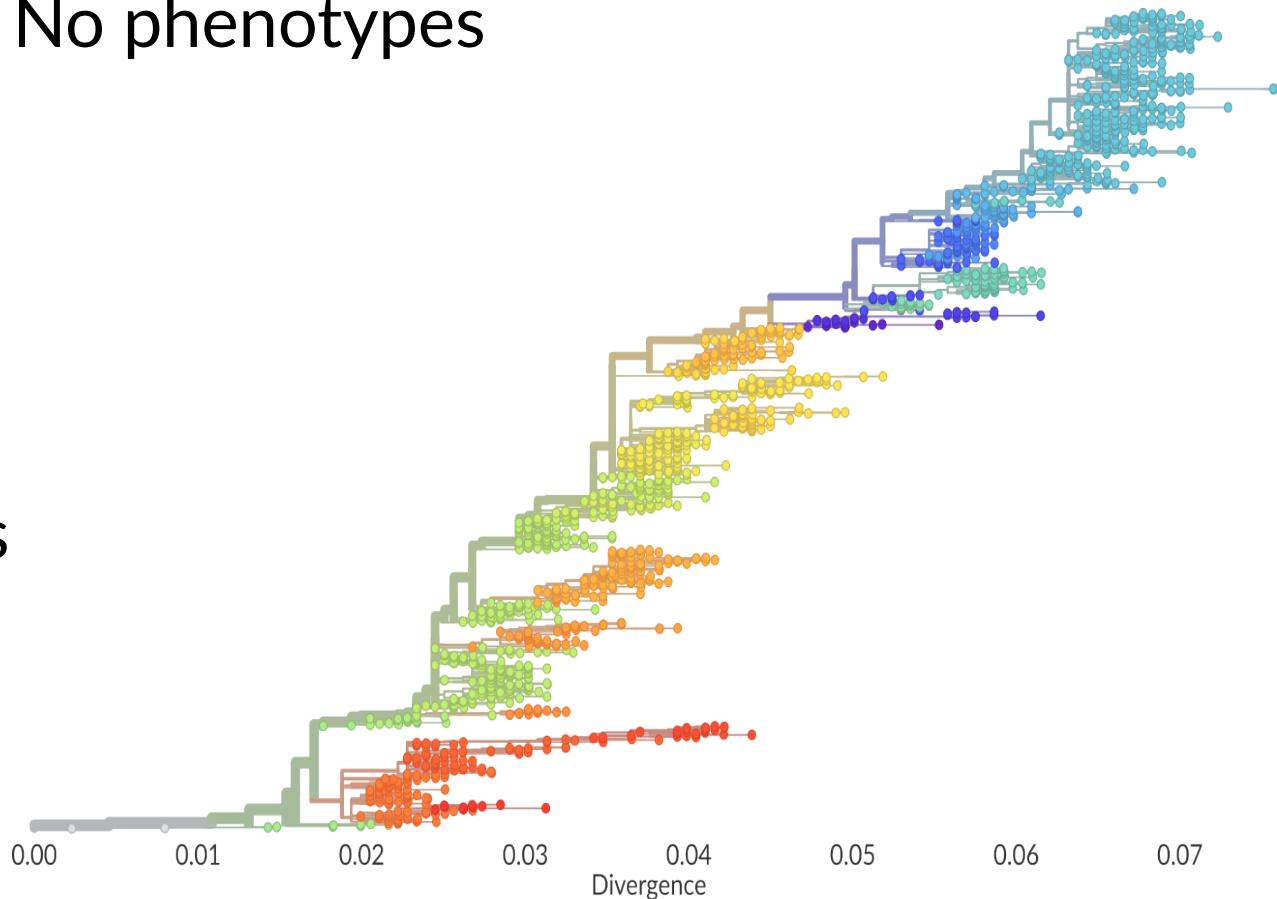


Limitations of purely genetic phylogenies

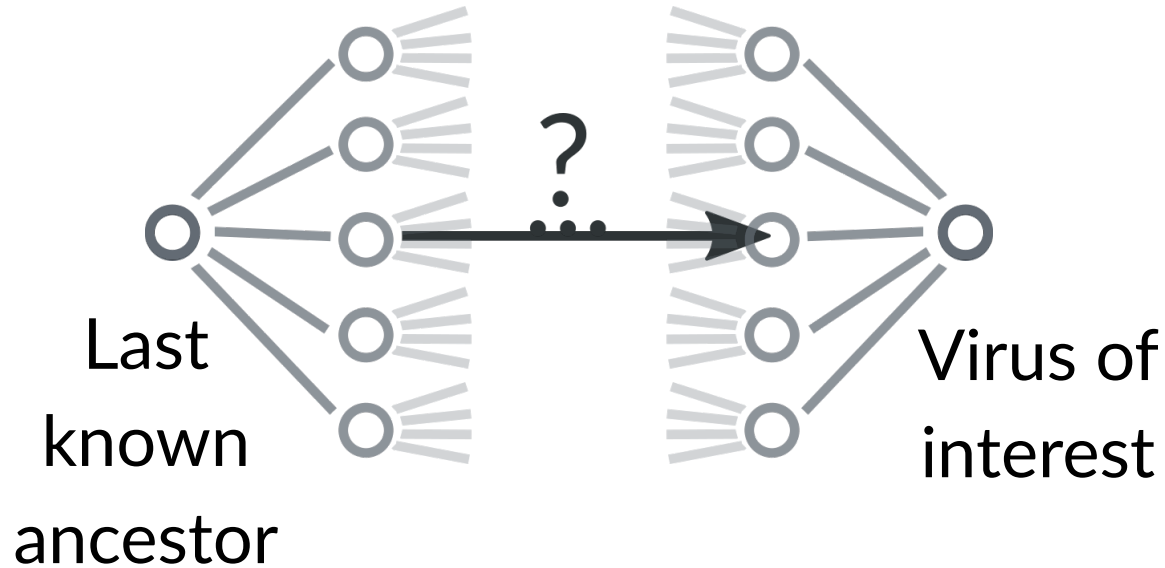
No phenotypes



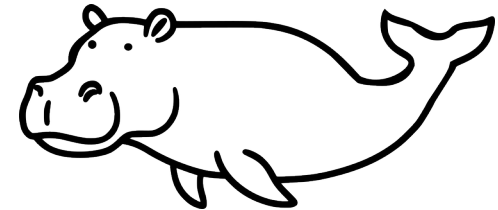
No fossils



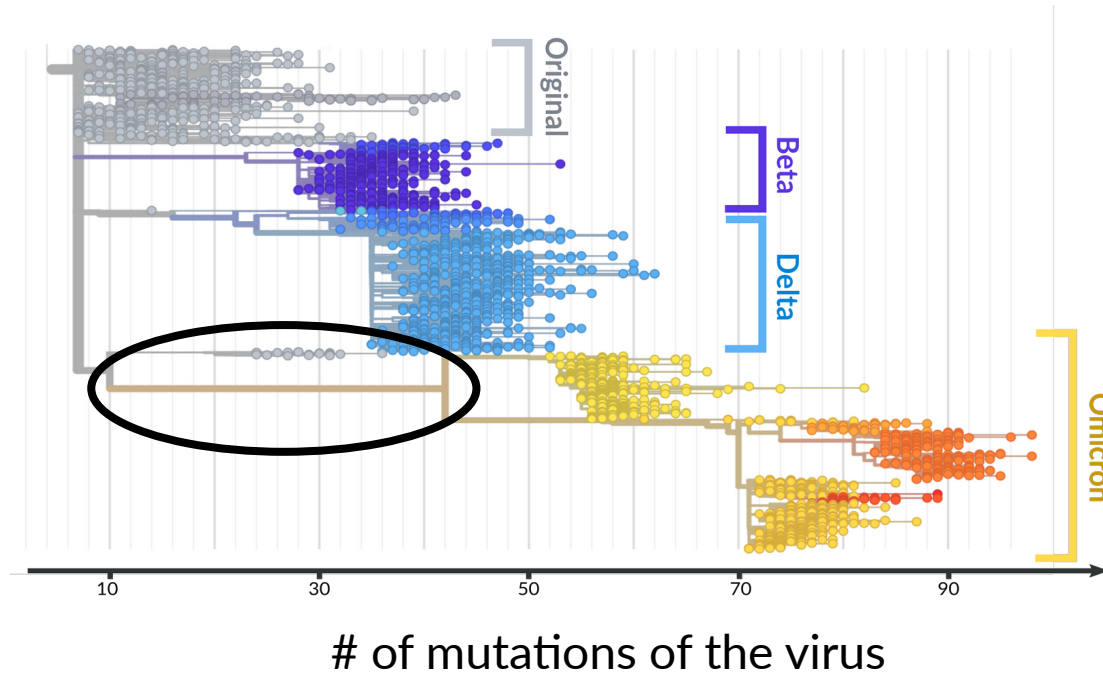
Viral paleontology



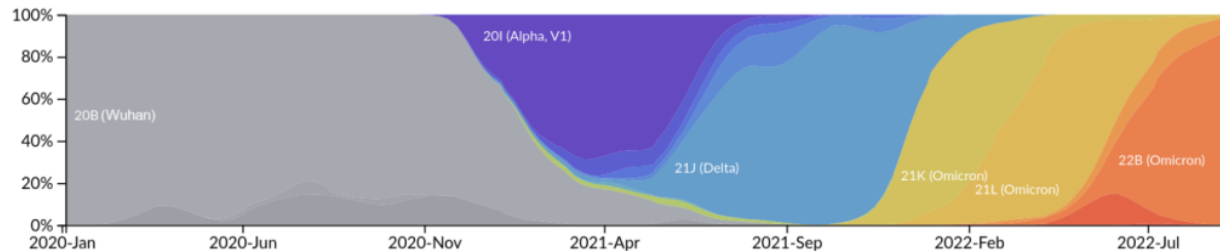
Reconstruct all possible intermediates, measure their phenotypes and infer the most likely path



Evolution of the SARS-CoV-2 Omicron variant

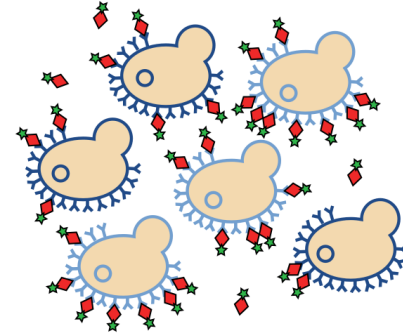


Omicron evolution happened within a small population and took a relatively long time.

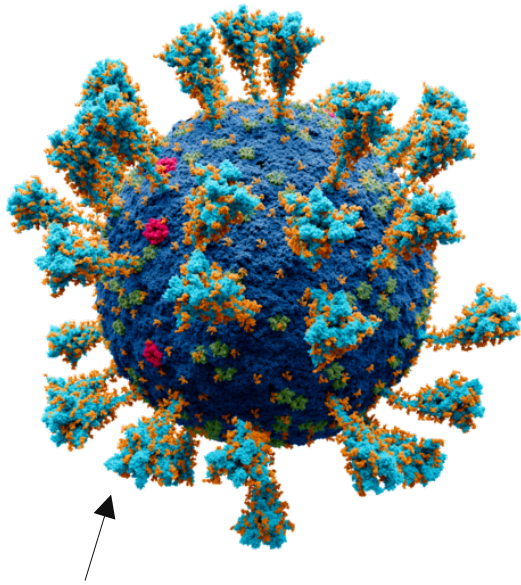


Affinity measurements for 2^{16} spike proteins

We measured the affinity of the spike proteins against 3 antibodies and the cell surface receptor, ACE2.

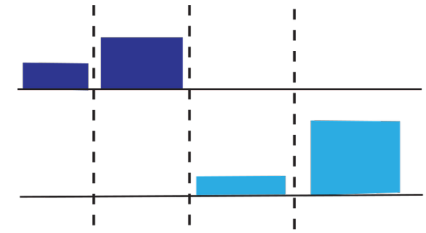


Expression on yeasts with fluorescent antigen



spike protein

Cell sorting, sequencing and statistics

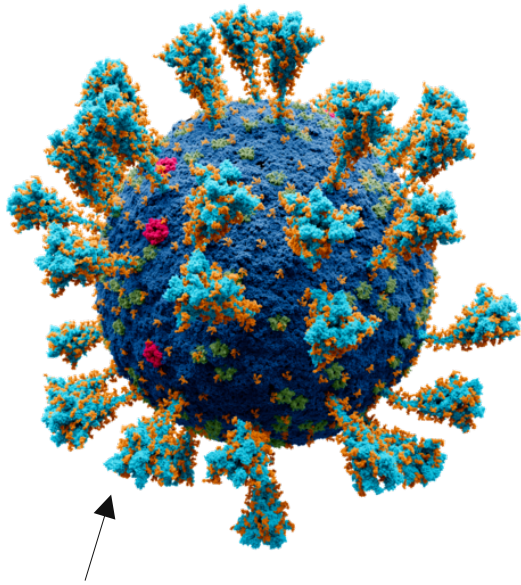


Extract binding affinities

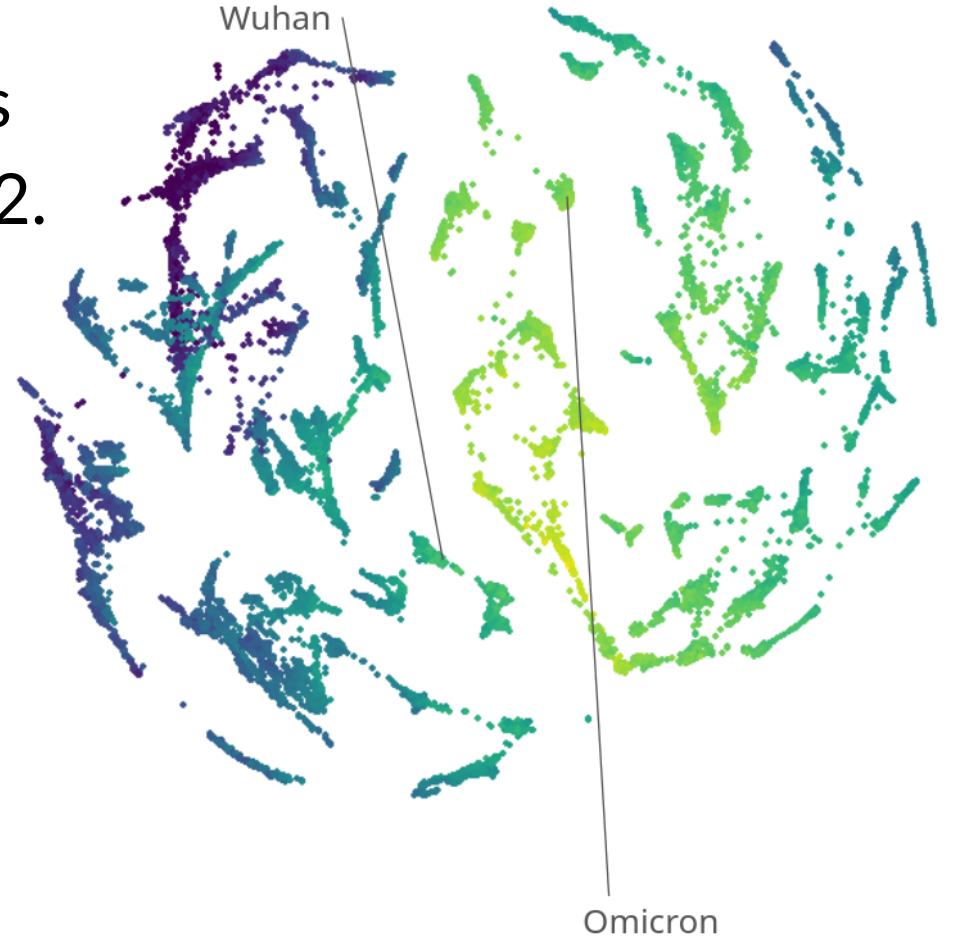
Concentration

Affinity measurements for 2¹⁶ spike proteins

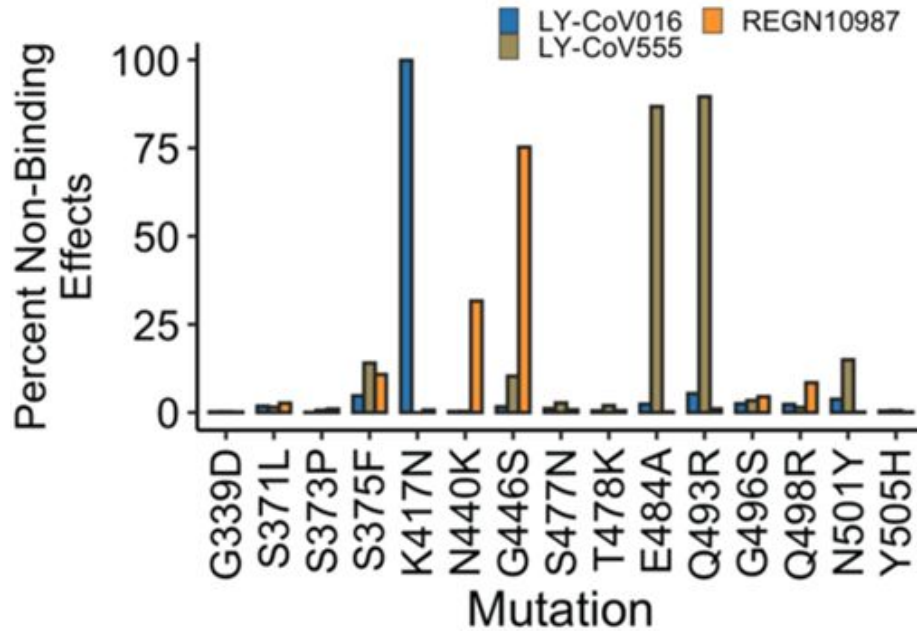
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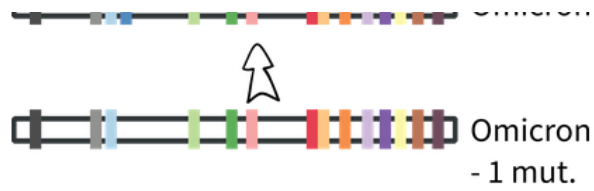
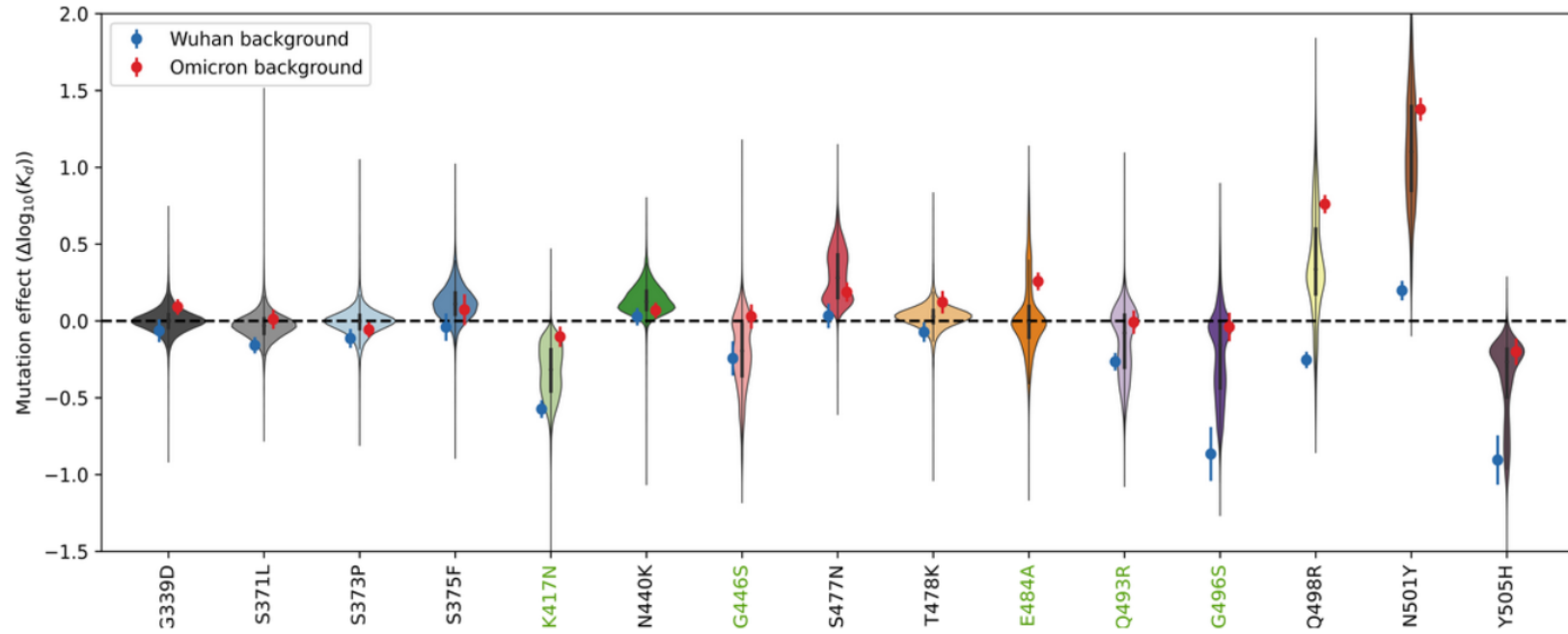
↑
spike protein



Antibody escape is mediated by few mutations

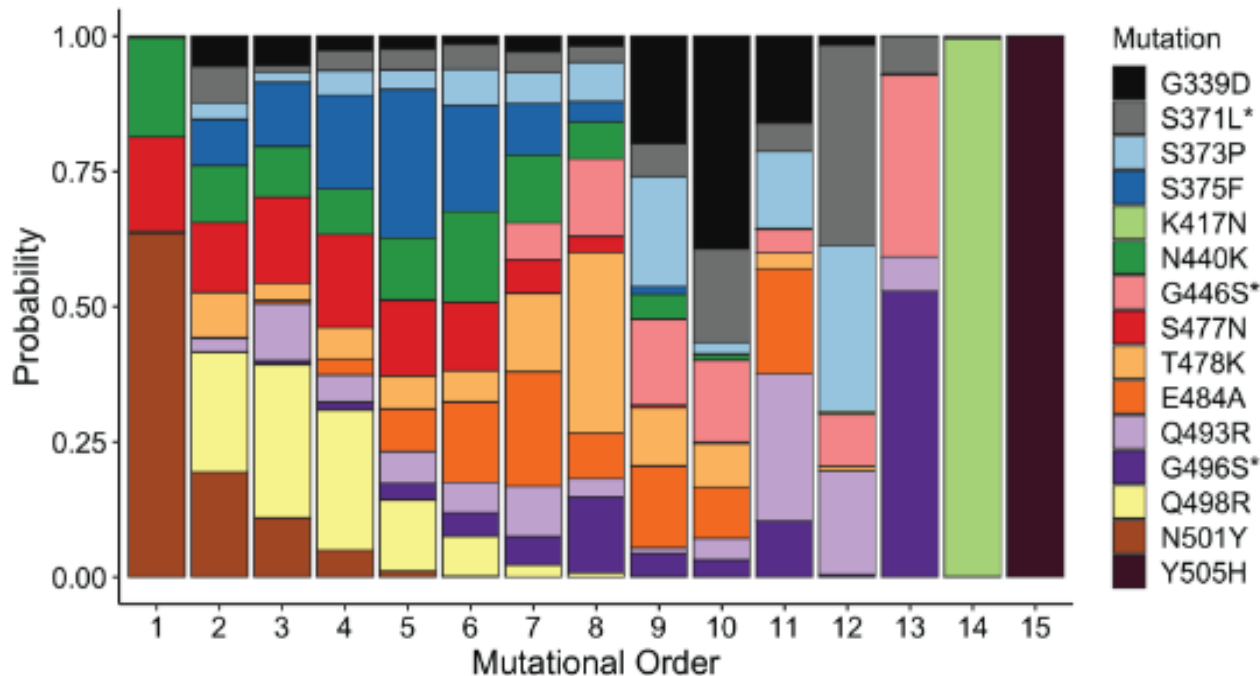


ACE2 binding landscape is complex

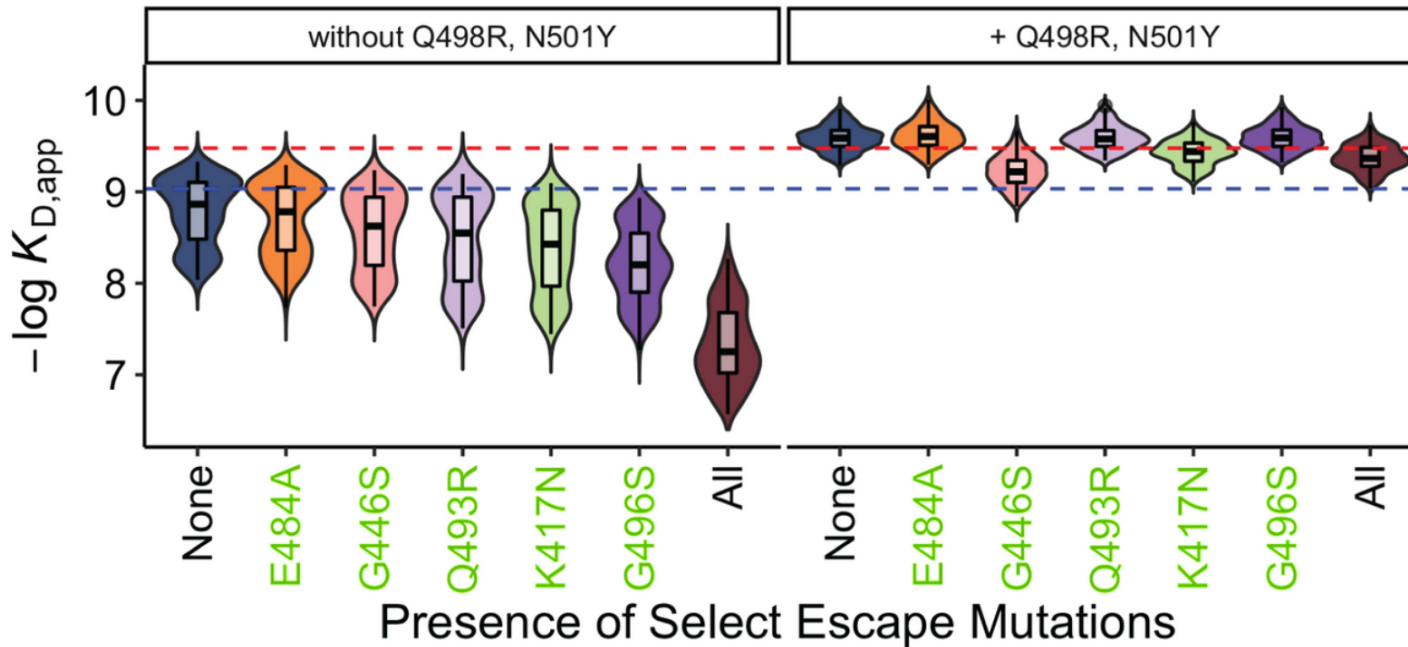


N501H & Q498R are likely to appear early

Simulating evolution

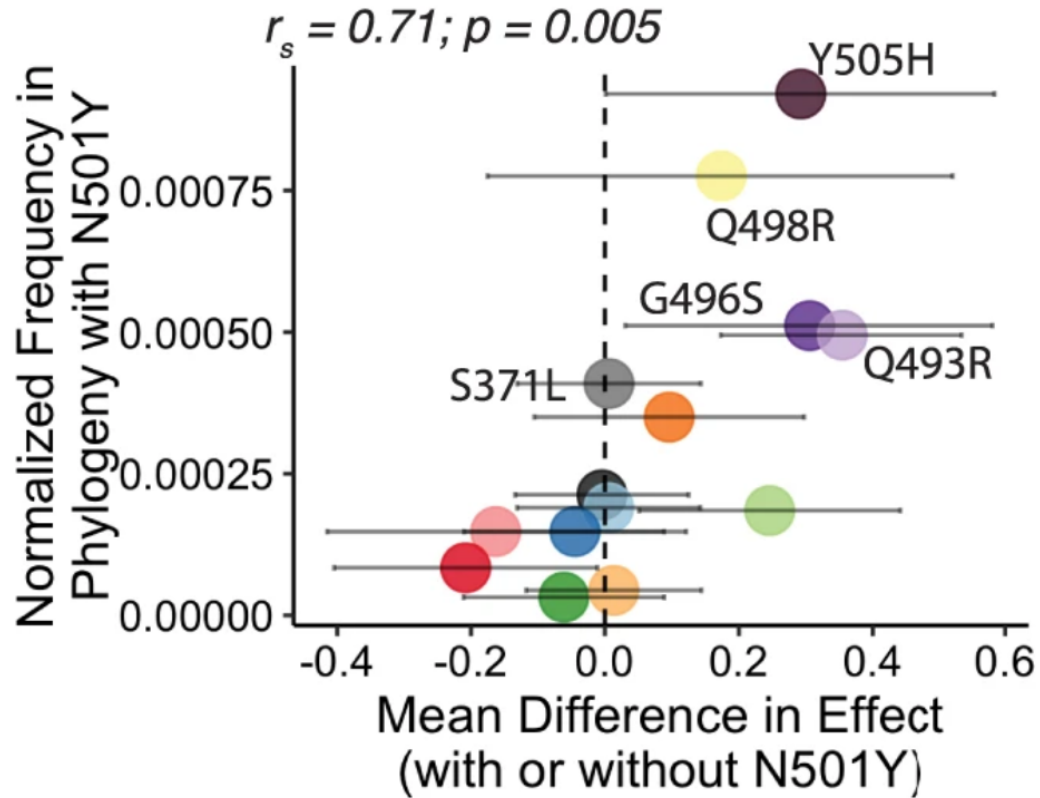


N501H & Q498R make viable the escape mutants

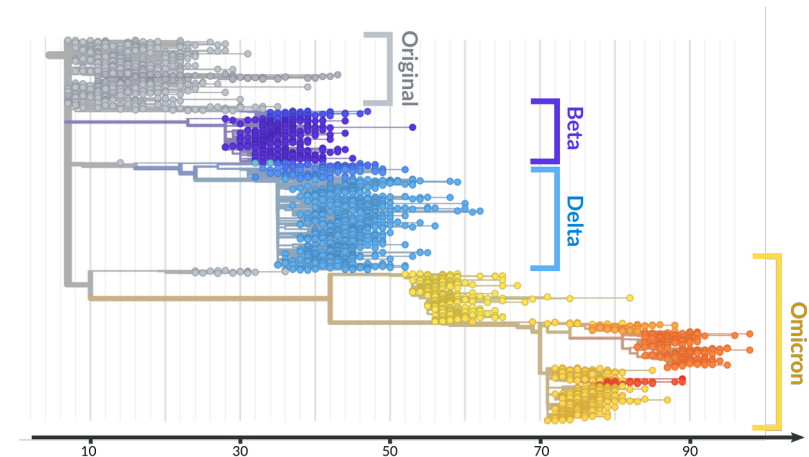


The same two mutations improve drastically the binding affinity of all immune-escape mutations.

Comparison with sequencing



Comparison with frequencies within the phylogeny.



Evolutionary landscape of Omicron



Ridge evolution against
ACE2



Cliff evolution against
antibodies

THANKS !

Tatiana Ruiz-Bedoya

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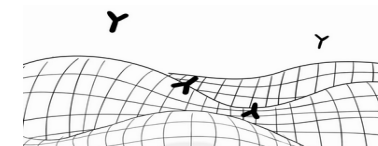
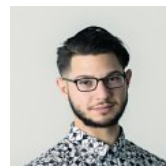
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Aleksandra Walczak



Available master
internship