Project C2, Heinrich Sticht

Structure-based design and optimisation of ligands for novel antiviral strategies

Broadly neutralizing antibodies that bind to viral fusion proteins represent a promising strategy for protection from viral infections. Such antibodies can be used for passive immunisation and are currently tested in clinical trials, but they are expensive and difficult to produce. As an alternative, antibody-derived peptides may be used for this purpose. In collaboration with the experimental group of Prof. Eichler (project C1), we aim to transfer the binding properties of neutralising antibodies to small peptide ligands.

For that purpose, the complexes between antibodies and fusion proteins from HIV-1 and CoV-2 are analyzed to identify energetic hot-spots of the interaction. This information will be used for the design of antibody-derived peptides that bind to viral fusion proteins thereby blocking viral infection. We have already developed a computational pipeline to identify the most promising peptides for further experimental testing.

The synthesis and experimental verification of the binding affinity of these ligands will be performed in the group of Prof. Eichler (project C1). Ligands that exhibit favourable properties will be further computationally optimised regarding their binding affinity and specificity. In this step, we will optimise the sequence to stabilise peptide conformation and to maximise intermolecular contacts.

To further enhance the functional properties, we plan to design hybrid ligands by combining high-affinity CDRs from different antibodies. A particular focus will be on those CDRs that contact spatially proximal regions of trimeric pre-fusion HIV-1 Env or CoV-2 Spike protein. This work will also include optimisation of the length and flexibility of the connecting linkers. The structural properties of all constructs will be further verified by molecular dynamics simulations and then be subjected to experimental validation by the experimental groups of this research collaborative. Taken together, we expect that the strategy outlined above will allow the design of peptides that are capable to interfere with the virus-host interaction.