Identification and structural characterization of peptidic ligands for novel antiviral strategies against SARS-CoV-2

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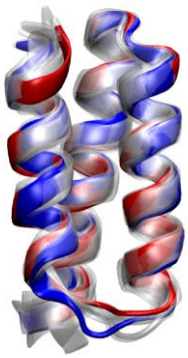
The COVID-19 pandemic, caused by the emergence of SARS-CoV-2, has not only engendered unprecedented global health challenges but has also underscored the urgent necessity for innovative antiviral therapeutic agents [1]. Antiviral peptides are fast-growing class of new drugs and are promising candidates for drug design.

Our study attempts to use the principles of structure-based computational drug design to engineer and refine antiviral peptides with a specific focus on targeting the Spike protein of SARS-CoV-2. The Spike protein plays a key role in viral entry and fusion and presents an enticing target for therapeutic intervention due to its pivotal role in facilitating viral infectivity [2].
To this end, we apply a multifaceted approach for peptide design that relies on the miniaturization of antibodies or other Spike-binding proteins (e.g. LCB1) [3].

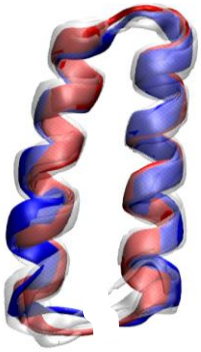
By using computational techniques, particularly molecular dynamics (MD) simulations, we do not only characterize the bound state of these peptides, but also their conformational stability prior to binding.

The dynamics of peptides in their free states has a significant impact their subsequent interactions with target structures because the formation of stable binding-incompetent conformations may hamper the interaction with target proteins.

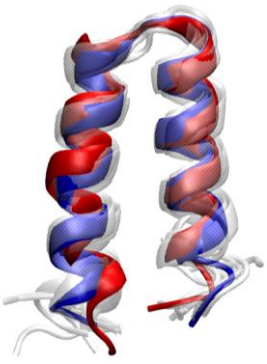
Preliminary findings from our MD investigations show a relationship between conformational stability of the free peptides and their ability to bind their target structures. This finding underscores that a comprehensive characterization of designed peptide ligands should also include an investigation of the unbound state.



LCB1



S-S bond (LW25.13)



Open form (LW25.1)

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3. Weißenborn L, Richel E, Hüseman H, Welzer J, Beck S, Schäfer S, Sticht H, Überla K, Eichler J. Smaller, Stronger, More Stable: Peptide Variants of a SARS-CoV-2 Neutralizing Miniprotein. Int J Mol Sci. 2022