Optimization of antibodies as therapeutics against COV2 infections

Development of a genetic algorithm for the optimization of COV2 neutralizing antibodies.

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In Short

- Enhanced Molecular Dynamics simulations.
- Investigations on the loop flexibility of strongly neutralizing antibodies (AB) against COV2.
- Investigations on the conformational landscape of the COV2 receptor binding domain (COV2-RBD).
- Investigations on conformational changes upon mutation of COV2-RBD.
- Structural modeling of AB-COV2-RBD complexes.
- Development of an energetical affinity scoring scheme.
- Development of a genetic algorithm for the mutational optimization of ABs against COV2.
- Applications of the genetic algorithm on ABs against COV2.

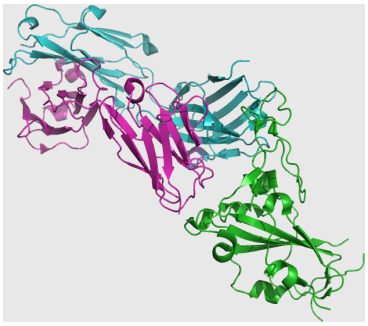

***Figure 1:** Antigen binding fragment B38 (violet, cyan color) isolated from the blood serum of a convalescent patient in complex with COV2 spike RBD (green color) (PDB : 7bz5).*

In 2019, a novel coronavirus (COV-2) has been identified as primary cause for the severe acute respiratory syndrome (SARS) resulting in a worldwide pandemic with millions of infections and hundreds of thousands of deaths. Before its world-wide spread, a first cluster of infections was located in Wuhan, China, where a first animal-to-human transmission occurred at the animal food market. Due to its high infectious potential, the lack of effective drugs and the high mortality rate among vulnerable individuals, the ongoing pandemic poses a world-wide economic and political threat. Despite worldwide vaccination efforts, there is a demand for effective treatment options of vulnerable individuals at the onset of the infection. Therefore, a detailed understanding of the molecular processes underlying human infection is necessary for the development of effective treatment strategies against COV2. A number of studies indicated that the viral entry into human cells depends on binding of the viral spike (S) proteins to cellular receptors and S-protein priming by host cell proteases [1]. The neutralizing antibody (AB) response to coronavirus infections acts primarily against the S-protein and the spike receptor-binding domain (RBD) [2,3] (see Figure 1). ABs and antigen binding fragments (Fabs) are a promising option for the treatment of COV-2 infections in vulnerable individuals at an early stage of Infection. Recent studies investigated the blood-sera of a large number of convalescent individuals, who were affected by a COV-2 infection [4]. The plasma of the convalescent individuals was tested for their neutralizing titer and polyclonal immunoglobulin Gs (IgGs) were isolated. A number of in silico studies treated the problem of the characterization of COV2-ACE2 interface and the dynamics of COV2 RBD at the viral activation process, while only few simulation studies tackled the problem of COV2 inhibition by strongly neutralizing ABs (snABs). In this project, we will probe the energetics of AB interactions at COV2-RBD and aim on the development of a computational pipeline for the optimization of AB-sequences as suitable therapeutics against COV2-infections. We will consider the wild-type of COV2-RBD (WT-COV2-RBD) and COV2-RBD mutants, which differ from WT-COV2-RBD in their infectious potential [10]. For the sufficient sampling of the phase space we will use a novel correlation guided enhanced sampling Molecular Dynamics (CORE-MD) method. We will combine protein docking and will identify AB-COV2 RBD structures, while we will consider the conformational heterogeneity of the AB loops, WT-COV2-RBD and mutants of COV2-RBD. We will develop an artificial intelligence network based on a genetic algorithm, while a detailed understanding of the energetics of snAB-COV2 binding is required in the first instance of the project. Therefore, a series of simulations is necessary to identify conformer clusters of snABs, WT-COV2-RBD and COV2-RBD mutants. Through an identification of snAB-COV2-RBD complexes, we will obtain a detailed understanding of the underlying structural determinants of snAB-COV2 binding and finally implement a computational pipeline for the tar-

geted optimization of snABs as suitable therapeutics against COV2-infections.

WWW

https://www.mhh.de/bpc

More Information

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