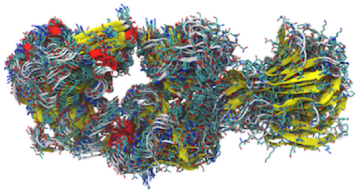

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In silico design of a new high-affinity antigen for HIV-1 2F5 antibodies

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Abstract:

To develop a vaccine against human immunodeficiency virus type 1 (HIV-1) is necessary the design of a immunogen that have the capacity to elicit potently neutralizing antibodies which are effective against a wide spectrum of HIV-1 strains [1]. The HIV-1 has evolved an arsenal of molecular tricks to avoid immune responses, including the transient exposure of key epitopes capable of triggering the production of broadly neutralizing antibodies, such as the 2F5 epitope [1]. The anti-2F5 antibody can neutralize over than 50% of viral isolated panels and protect primate models upon challenge [2]. We have previously engineered a chimerical protein where the 2F5 epitope was grafted onto Top7, a computationally devised protein [3]. The protein named Top7-2F5 was shown to be specifically recognized by the respective monoclonal antibody (mAb 2F5) by means of enzyme-linked immunosorbent assay (ELISA) [4] and presented significantly higher affinity to the mAb 2F5 than the actual gold standard peptide marker. In this work we aimed to improve the affinity of the Top7-2F5 protein for the mAb 2F5. To this aim the amino acids sequence of the Top7-2F5 was re-designed by means of a computational protein design protocol. In this protocol the antigen was docked to the 2F5 antibody structure. Along the docking steps, mutations were performed in the antigen around the epitope and binding site. The antigen-antibody affinity was improved by selecting the new antigen structure with the lowest free-energy of binding. The structural stability of the new antigen molecule was assessed through molecular dynamics simulation.

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