BIO_13 - Development of computational pipeline for antibody identification against specific conformations of PD-1

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Introduction: Programmed-cell death protein 1 (PD-1) is a recognized target for cancer immunotherapy. Currently, available therapeutics are focused on their interface with its natural ligand PD-L1. While the naïve antibody repertoire in human is estimated at $>10^{11}$, there are only thousands of solved structures. It is still challenging to predict the VH and VL relative orientation, and CDRH3 conformation.

Objective: We aimed to develop a new structure-based pipeline from the known structures for effective computational screening and optimization of antibody against distinct conformations of PD-1.

Methodology: Firstly, we have used molecular dynamics simulation (MD) and GaMD (Gaussian accelerated Molecular Dynamics), and the principal component analysis (PCA) for describing the conformational space of PD-1 in both apo and complexes states. In a second step, a representative antibody structure database was built based on the structural diversity of antibody CDRs described in PyIgClassify. CDRH3 loop was treat separately for further CDR crafting. Subsequently, a multistep protein docking and MD protocol, using Haddock and Amber18, respectively, was developed for identifying the suitable antibody. The interaction was optimized by evaluation of mutations proposed by mCSM-AB2 and BeatMusic webservers, using heated MD.

Results: We identified a new PD-1 conformation with the BC loop displaced from conventional conformation, forcing the FG loop toward the PD1-PDL1 interface, that would prevent the PD1-PDL1 binding. The selected CDRH3-crafted antibody, which is expected to stabilize the BC loop, already showed good docking results against PD-1, but the optimized structure yielded even more satisfactory results. The optimized PD1-antibody complex also showed excellent stability during heated MD ($RMSD_{interface} \sim 6Å$) consistent with the observed in literature. Finally, the modified antibody does not recognize the original antigen, since while the original antibody had its correct pose readily identified, by docking, the mutated antibody not even generated the crystallographic pose.

Conclusion: Here we described and applied a new protocol for computationally design new antibodies taking advantage of the structural variability of CDRs loops at low computational cost.

Keywords: Antibody screening; PD-1; Bioinformatics