Design of Antibody-based Peptide Inhibitors to Disrupt Important Protein-Protein Interactions in HIV and HCMV

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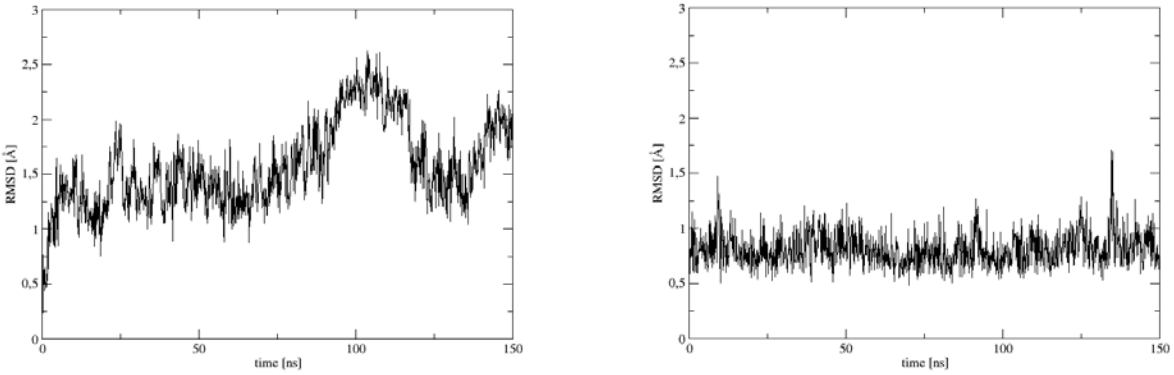

Over the last decades the versatility and quality of computational techniques, such as docking, high throughput virtual screening, and molecular dynamics (MD), as a tool in Drug Discovery and protein research have increased considerably. One promising approach on the development of new drugs is the computer supported design of peptides as protein binding site mimetics [1].

Some antibodies, such as anti-HIV antibody b12 [2] or anti-HCMV antibody SM5-1 [3] competitively bind to epitopes that are essential for the pathogens' entry into the cell, thus encumbering the infection. The complementarity determining regions (CDR) of these and several other antibodies were used as basis for the design of peptidic ligands to their respective antigens.

To ensure that these peptides retain the conformation they take up in the antibodies head-to-tail cyclization and disulfide bridges were utilized as stabilizing measures. The figure above illustrates the effectiveness of artificial disulfide bonds: The left plot shows the RMSD of CDR H3 of SM5-1 without any modifications, the right plot depicts the RMSD of a construct with disulfide bond.

By using those principals on several anti-HIV and anti-HCMV antibodies, and also introducing point mutations into the peptides, antigen binding ligands could be discovered. However, in order to create peptides rivaling the antibodies' binding affinity further refinement is necessary.

[1] J. Eichler, *Current Opinion in Chemical Biology*, **2008**, *12*, 707-713.
[2] T. Zhou, L. Xu, B. Dey, A. Hessel, D. Van Ryk, S-H. Xiang, X. Yang, M. B. Zwick, J. Arthos, D. R. Burton, D. S. Dimitrov, J. Sodroski, R. Wyatt, G. J. Nabel, P. D. Kwong, *Nature*, **2007**, *445*, 732-737.
[3] S. Pötzsch, N. Spindler, A. K. Wiegler, T. Fisch, P. Rucker, H. Sticht, *PLOS Pathogen*, **2011**, *7*, e1002172.