In silico affinity optimization of modified peptides using non-natural amino acids

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Bioactive peptide conformations can be stabilized by macrocyclization resulting in increased target affinity and activity. In this regard, a 12mer peptide from the C-terminal end of Pseudomonas aeruginosa virulence factor exoenzyme S binding to its human adaptor protein 14-3-3 was stabilized by introduction of a hydrophobic cross-link,[1] thus providing the basis for *in silico* optimization.

Computational protein-peptide docking is still a challenging task because exposed solvent plays an important role in protein-protein interfaces and water is usually not considered during docking. More important, long peptides imply a large number of computational degrees of freedom where current docking approaches reach their limit.[2] Beside these docking limitations, currently available computational approaches for peptide affinity optimization are only based on the 20 canonical amino acids.

In this work, we try to overcome these issues by (1) developing a molecular docking strategy suitable to handle large peptide ligands, and (2) optimizing the affinity of modified peptides by introducing side-chain mutations from a library of non-natural amino acids.

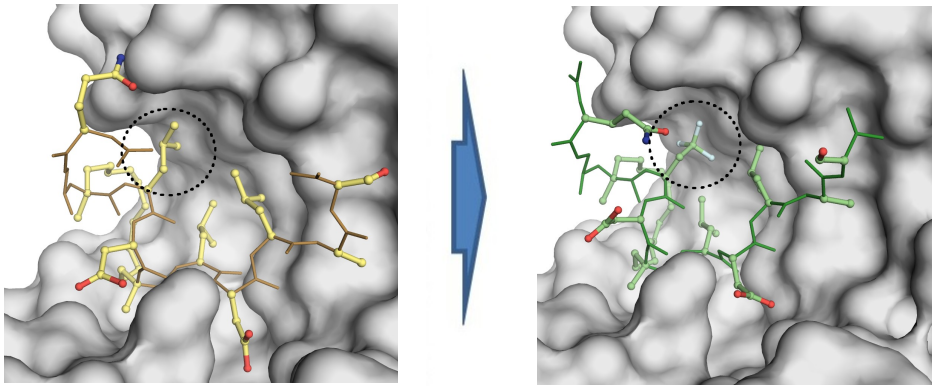

Figure: Residue-based screening of a library of non-natural amino acids by peptide-adapted molecular docking leads to optimized modified peptides with improved affinity.

Left: X-ray structure depicted in yellow. Right: docking prediction depicted in green.

[1] Glas, A., Bier, D., Hahne, G., Rademacher, C., Ottmann, C., Grossmann, T., *Angew. Chem.*, **2014**, *53(9)*,2489-93.

[2] Krüger, D.M., Jessen, G., Gohlke, H., *JCIM*, **2012**, *52(11)*, 2807-11.