PEPTIDE SELF ASSEMBLY CONFERENCE 2026
MAINZ. GERMANY
FROM DYNAMIC STRUCTURES TO FUNCTIONAL MATERIALS

Novel Peptide Targeting CXCR4: Rational Design and characterization through Computational Modeling

J. Vieyto-Nuñez[1], Y. Almeida-Hernández[1], D. Albers[2], J. Münch[2], M. Harms[2], E. Sanchez-Garcia[1]

[1] Department of Biochemical and Chemical Engineering, Technical University Dortmund, 44227, Germany
[2] Institute of Molecular Virology, Ulm University Medical Center, Ulm, 89081, Germany

Given its role in immune cell trafficking and cancer metastasis, CXCR4 represents a promising target for the development of peptide-based antagonists. Recent evidence showed a connection between the G Protein-Coupled Receptor 15 Ligand (GPR15LG) and CXCR4 signalling, prompting us to design GPR15LG-derived peptides to target CXCR4. Starting from the full-length GPR15LG, we performed Gaussian accelerated molecular dynamics (GaMD) simulations as enhanced sampling technique to explore its binding to CXCR4 receptor. These results guided the design of an N-terminal peptide derivative, GPR15LG-N, which exhibited conserved binding to CXCR4. Using energy-reweighted potential of mean force (PMF) maps we identified the main binding mode of GPR15LG-N, which is characterized by cooperative ion-pair contacts between the peptide ^{35}RRTR^{38} motif and acidic pocket residues D187, D262, and E277 (Figure 1). Alanine mutations at the N-terminal latch (D20/D22) increased pose heterogeneity and promoted off-site binding. Additionally, we ranked the peptide variants using PPI-Affinity, our machine-learning tool, and identified key residues for the interaction interface. Ultimately, this integrated *in silico* framework combines GaMD simulations with machine-learning predictions to streamline the identification and engineering of therapeutic peptide derivatives.

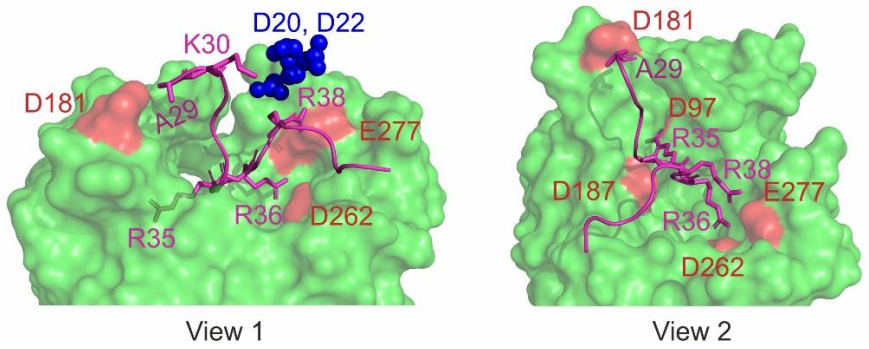

Figure 1. Main binding mode of GPR15LG-N peptide (purple cartoon) with the CXCR4 receptor (green surface) obtained from enhanced sampling simulations.