HOX protein

HOX proteins have been extensively studied due to their pivotal role in transcriptional events. HOX proteins execute their activity by exploiting a cooperative binding to PBX proteins and DNA. Therefore, an increase or decrease in HOX activity has been associated with both solid and hematological cancer diseases. Thus, inhibiting HOX-PBX interaction represents a potential strategy to prevent these malignancies, as demonstrated by the patented peptide HTL001 that is being studied in clinical trials. In this work, a computational study is described to identify novel potential peptides designed by employing a database of non-natural amino acids. For this purpose, residue scanning of the HOX minimal active sequence was performed to select the mutations to be further processed. According to these results, the peptides were point-mutated and used for Molecular Dynamics (MD) simulations in complex with PBX1 protein and DNA to evaluate complex binding stability. MM-GBSA calculations of the resulting MD trajectories were exploited to guide the selection of the most promising mutations that were exploited to generate twelve combinatorial peptides. Finally, the latter peptides in complex with PBX1 protein and DNA were exploited to run MD simulations and the ΔGbinding average values of the complexes were calculated. Thus, the analysis of the results highlighted eleven combinatorial peptides that will be considered for further assays [1].

1)
Gulotta MR, De Simone G, John J, Perricone U, Brancale A. A Computer-Based Methodology to Design Non-Standard Peptides Potentially Able to Prevent HOX-PBX1-Associated Cancer Diseases. Int J Mol Sci. 2021 May 26;22(11):5670. doi: 10.3390/ijms22115670. PMID: 34073517; PMCID: PMC8198631.