Designing a High-Affinity Peptide Binder to the BRD4 ET Domain to Outcompete MLV TP Utilizing ProteinMPNN and AF-CBA With Additional Molecular Dynamics Verification

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Classified under the Bromodomain-Extra Terminal family, Brd4 plays a crucial role in the transcriptional activation of genes involved in immunity, leading to sterile inflammation and fibrosis. Brd4 recruits cellular partners for gene expression, utilizing the extra-terminal (ET) domain to facilitate transcriptional activation. The retroviral murine leukemia virus tail peptide (MLV TP), has developed a higher affinity binding structure to ET, resulting in the transcriptional upregulation of protooncogenes and leukemia development. However, the proteome's inherent intricacy, characterized by diverse protein-protein interactions, complicates the identification of therapeutic binders for protein domains. Therefore, the focus is to design a theoretical peptide candidate that outcompetes MLV TP using ProteinMPNN, with a mathematical framework to predict peptide configurations. This is complemented by verifying the peptide's physical characteristics to derive an optimal inhibitor through physics-based Molecular Dynamics (MD). Alphafold's (AF) Competitive Binding Assay was utilized to filter out hundreds of peptides that are incapable of outcompeting MLV TP based on AF confidence metrics, such as predicted Local Distance Difference Test, Predicted Aligned Error, and predicted template modeling. A pool of candidate binders outcompeting MLV TP from 5 simulations will participate in an all-by-all competition, where the top prediction ProteinMPNN-generated peptide M466 was identified. Ultimately, MD metric RMSD/RMSF, coupled with Newtonian mechanics, verified structural change and overall stability of peptide M466. Discovering optimal peptide binders in silico serves as the basis for peptidomimetic design, allowing for efficacy in drug therapeutics and inhibiting disease models.

Awards Won:
Fourth Award of $600