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Deep-learning Based Design of Peptide Binders Targeting Pan-KRAS Variants

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Pancreatic cancer is one of the most lethal malignancies worldwide, with a high mortality rate due to limited drug development and therapeutic strategy from genetic complexity of the disease. KRAS, a central oncogene in human pancreatic tumorigenesis, harbors recurrent mutational hotspots, with substitutions at glycine 12 position being the most frequent in pancreatic cancer. These alterations hinder therapeutic strategies, by generating substantial heterogeneity. Targeted small molecule drugs, including Sotorasib and MRTX1133, have been developed to suppress specific KRAS mutants. However, their efficacy is restricted due to resistance arising from secondary mutations upon targeting a single mutation. We designed peptide binders against diverse KRAS variants using a pipeline integrating RFDiffusion, ProteinMPNN, and Rosetta, widely used in protein design. Structural analysis of the KRAS complex (PDB ID: 9AX6) with PyMOL revealed the interaction residues of RMC-6236, a small-molecule inhibitor targeting multiple KRAS variants. Building on these findings, we sought to develop a peptide binder that first forms a binary complex with immunophilin and subsequently recruits activated KRAS into the tri-complex. Using RFDiffusion, we generated 1,000 backbone models for cyclic peptide binders. ProteinMPNN was then employed to design three distinct amino acid sequences per backbone, tailored to engage the target protein. Among these, the top-scoring sequences were selected and subjected to Rosetta, yielding a library of refined complexes. Predicted complex structures from AlphaFold were subsequently assessed using PAE, pLDDT, and RMSD to prioritize promising binders. Finally, docking simulations were performed, and the PSL-01 was identified based on its differential binding affinity toward the target compared with the control. These findings highlight the promising potential of a peptide therapeutic targeting multiple KRAS mutations in pancreatic cancer. Our study underscores a deep learning–based strategy to substitute conventional small-molecule agents—which often elicit adverse effects owing to limited specificity and stability—with high-affinity, physiochemically stable peptide drugs.