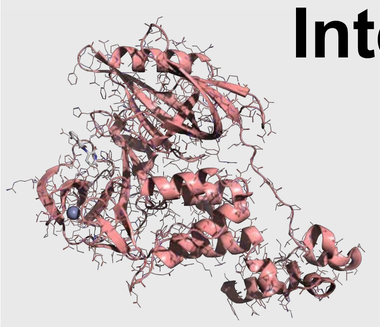
Molecular Glues in Drug Design: Enhancing Protein-Protein Interaction Stability for Innovative Cancer Therapies



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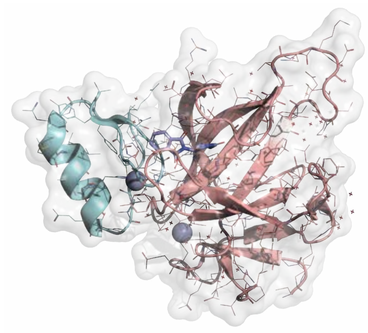
Computational Molecular Design

Abstract

Molecular glues (MGs) have the potential to revolutionize medicinal chemistry and drug design by stabilizing protein-protein interactions (PPIs), leading to novel therapeutic strategies. Understanding how MGs enhance PPI stability is crucial for harnessing their full potential. Our research aims to uncover the physicochemical principles behind MG interactions and integrate these insights into computational tools for identifying small molecules that stabilize ternary complexes.

As a case study, we focus on the E3 ligase Cereblon (CRBN), a pivotal protein in targeted protein degradation (TPD). Building on findings that lenalidomide enhances the stability of the CRBN-CK1α complex by strengthening hydrogen bonds, our work aims to advance innovative anticancer strategies by discovering small molecules that can selectively degrade proteins overexpressed in cancer.

Objective



To unravel the physicochemical determinants that govern how MGs stabilize protein-protein interfaces, providing insights into the mechanisms by which these molecules enhance binding affinity and specificity.

Computational Methods and Workflow overview

1 System Preparation

The different PPIs were modelled using the available structures of the CRBN-neosubstrate complexes in the PDB. For CRBN protein partners not available in the PDB, we used predicted structures from the AlphaFold Protein Structure Database.

We employed the ff14SB and gaff2 force fields to describe the proteins and ligands, respectively, ensuring accurate representation of their interactions.

AMBER MD

2 pyMDmix[2]

Pharmacophoric restraints were identified by incorporating organic solvents into the solvation box, which helped mimic a diverse chemical environment. This approach allowed us to detect interaction hotspots to be used in the subsequent VS campaigns.

MDs were performed using the AMBER22 package.

pyMDMix

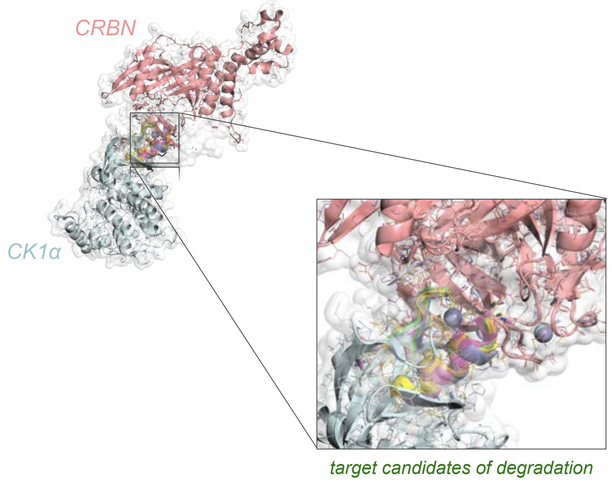
3 Virtual Screening (VS)

VS campaings were performed with the rDock software, applying pharmacophoric restraints that targeted potentially relevant H-bond donors and acceptors.[3]
This approach helped in identifying compounds that could potentially stabilize the CRBN-neosubstrate interactions by forming or reinforcing crucial hydrogen bonds. The compound library explored was the CRBN-focused collection from Enamine.

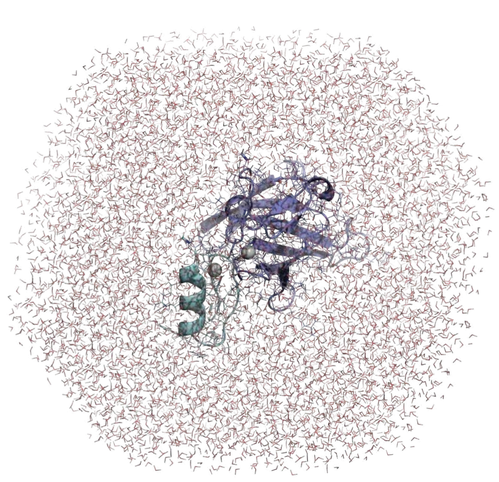
rDock

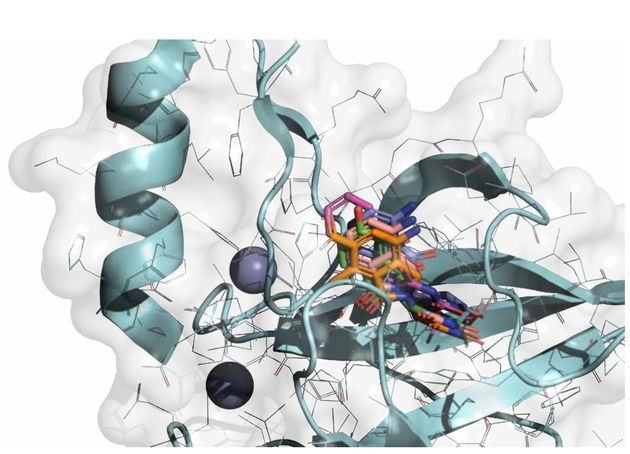
4 Steered Molecular Dynamics (SMD)

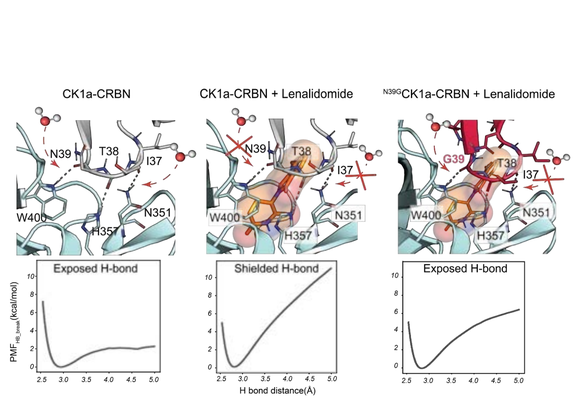
Using SMD[4] and the Jarzynski equality, we seek to determine Potentials of Mean Force (PMF) along the breaking of selected H-bonds at protein-protein interfaces. Understanding the impact of small molecules on those H-bonds will be a first step towards the rational discovery of MGs. This analysis will reveal key interactions for targeted therapeutic development and help correlate computational predictions with experimental binding affinities, guiding the design of more effective MGs.



target candidates of degradation



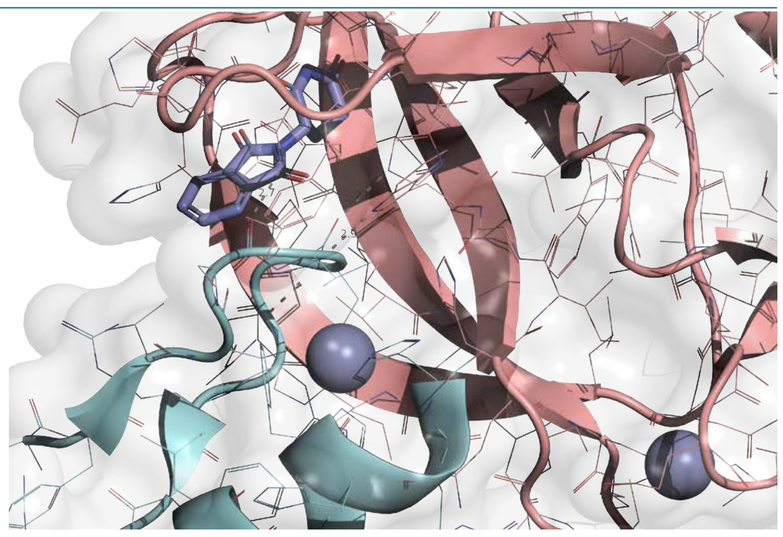




Expected impact of the results

The development of molecular glues (MGs) is moving from serendipitous discoveries to rational approaches that leverage the molecular mechanisms of ligand-induced stabilization of protein-protein interactions.

Building on our previous work[1], which explained the stabilization of the CRBN-CK1a interface by lenalidomide, we aim to discover new MG families for modulating other proteins involved in oncological processes and develop a web server mapping protein similarities to pharmacophoric hotspots, which will benefit a broad range of scientists and advance next-generation therapeutics.



Conclusions

- **Stabilization of PPIs**. Molecular glues significantly stabilize the CRBN-CK1α protein complex by enhancing hydrogen bond strength.
- **Targeted Protein Degradation.** This stabilization is critical for inducing the degradation of proteins overexpressed in cancer, offering a promising therapeutic approach.
- **Integration into Computational Tools.** Understanding the physicochemical principles of MG interactions allows for the development of computational tools to identify new molecular glues.
- **Innovative Anticancer Therapies.** Our findings support the potential of molecular glues to revolutionize anticancer drug design and therapy.
- **Future Research Directions**. Continued exploration of molecular glue candidates and their applications in different cancers is essential for advancing therapeutic strategies.

References

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