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SUMMARY of
FY2024 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, Osaka University

Research Title		Development of an in-silico design protocol of peptide inhibitors for protein-protein interactions
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Summary

Protein-protein interactions (PPIs) are central to biological regulation and disease pathways, yet they remain challenging to target with small molecules due to their large, shallow interaction surfaces. Peptide inhibitors offer a promising alternative by mimicking natural binding motifs. However, the diversity of peptide sequences and structures complicates the rational design of effective inhibitors.

This study presents a novel, structure-based, interpretable machine learning (ML) framework for identifying peptide inhibitors targeting PPIs, with a focus on the SARS-CoV-2 receptor-binding domain (RBD). A random forest classifier was trained using over 6,500 peptide-protein complexes from the BioLip2 database. Key features included amino acid triads extracted from residue interaction networks (RINs), transformed into physicochemical interaction profiles. The resulting model achieved 77.2% accuracy and 98.3% specificity in identifying binding residues.

This high-specificity model was then employed in a virtual screening of over 3,300 antimicrobial peptides from the DRAMP 3.0 database, targeting the RBD of the BA.2.86 SARS-CoV-2 variant. Ten peptides with promising predicted binding residues were selected. Among them, the 9-mer Jellein-2 (TPFKISIHL), derived from honeybee royal jelly, showed the highest binding affinity. Molecular docking confirmed strong interactions at conserved RBD epitopes, and further atomistic molecular dynamics (MD) simulations and MM/GBSA binding energy analyses validated the stability and energetics of Jellein-2's binding, particularly at Class 1, 3, and 5 epitopes.

Feature importance analysis of the ML model revealed that non-polar aliphatic side chains were crucial for effective binding, aligning with the physicochemical profile of Jellein-2. The peptide's alternating hydrophobic–hydrophilic pattern enables it to engage receptor surfaces while maintaining solubility.

This research establishes a generalizable in-silico protocol that integrates machine learning, virtual screening, and molecular modeling for the design of peptide inhibitors. Jellein-2 is proposed as a potential lead for antiviral development, and the protocol is adaptable to other PPI systems beyond SARS-CoV-2.