DATE: 11/05/2026

SUMMARY of
FY2025 RESEARCH RESULTS REPORT
For International Collaborative Research with IPR, The University of Osaka

Research Title		Computational Exploration of the Conformational Landscape Underlying the Function of the FABD-like Domain in HEV Polyprotein
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	Present Title	**Researcher (Principal Investigator)**
Research Collaborator (Host PI)		**Sandhya P. Tiwari**

Summary

The replication machinery of the Hepatitis E virus (HEV) remains poorly understood. Recently, our structural analyses of over 1,200 sequences redefined the HEV ORF1 polyprotein (pORF1) as a five-domain architecture. While this collaborative visit originally aimed to explore the conformational dynamics of the conserved FABD-like domain within pORF1, experimental delays in our home laboratory prompted a strategic pivot. We instead redirected our computational efforts toward two high-impact projects: characterizing the newly identified "domain X" (X-macrodomain) in pORF1, and investigating the interaction between the disordered HEV ORF3 protein and the host enzyme ZDHHC17.

Using AlphaFold2 structural modeling combined with Molecular Dynamics (MD) simulations analyzed via our custom TTClust program, we examined the pORF1 X-macrodomain. High-temperature (400K) simulations yielded a breakthrough discovery: the "original" X-macrodomain is structurally degenerated and unstable, whereas a newly identified duplicated macrodomain acts as the functional, stable unit. This paradigm-shifting finding fundamentally updates HEV replication models, and a manuscript detailing these results is in preparation.

Concurrently, in collaboration with the University of Heidelberg, we modeled the interaction between the largely disordered HEV ORF3 and human palmitoyltransferase ZDHHC17. Classical MD simulations validated the structural stability of the complex over time, confirming a distinct binding motif within ORF3 that stably interacts with the host enzyme. A manuscript on this collaborative work is nearing submission this month.

Moving forward, we will return to the FABD-like domain, armed with new insights from an expanded evolutionary analysis. We recently uncovered a striking divergence: the full FABD-like domain is exclusive to human-infecting strains (Paslahepeviridae), whereas rat-infecting (Rocahepeviridae) and bat-infecting (Chirohepeviridae) strains possess only small helices or a small beta-barrel in this region, respectively. Our future computational work will simulate these diverse structures to determine their specific roles (such as membrane interaction or protein-protein recognition) and uncover how these structural variations drive viral replication and host-specificity across different species.

***Deadline: May 11, 2026**
***Please submit it to E-mail: tanpakuken-kyoten@office.osaka-u.ac.jp.**
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